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Horemans, H.L.D.

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# Pyridostigmine Treatment in Postpoliomyelitis Syndrome

The studies presented in this thesis were carried out at the department of Rehabilitation Medicine of the VU University Medical Centre Amsterdam, the department of Clinical Neurophysiology of the University Medical Centre Nijmegen, and the department of Rehabilitation Medicine of the Erasmus Medical Centre Rotterdam.

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VRIJE UNIVERSITEIT

# Pyridostigmine Treatment in Postpoliomyelitis Syndrome

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op gezag van de rector magnificus  
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Henricus Leonardus Dingeman Horemans

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promotoren:    prof.dr. F. Nollet  
                  prof.dr. G.J. Lankhorst

copromotor:    dr. J.A.J.M. Beelen

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# CHAPTER 1

Introduction





## The Postpoliomyelitis Syndrome

Poliomyelitis, or infantile paralysis, is an infectious viral disease that causes an acute, flaccid paresis of a varying number of muscle groups.<sup>1</sup> Large epidemics occurred in the first half of the 20th century and affected mainly children under the age of five. In the mid-fifties vaccination became available, and although polio persisted in the developing countries, it became a 'forgotten' disease in the Western world.

Although cases of late onset progressive muscle weakness following polio had occasionally been reported since the end of the 19<sup>th</sup> century,<sup>2</sup> it was generally assumed that the residual neurological deficits resulting from polio would remain stable throughout life. However, in the late nineteen seventies large numbers of polio survivors of the epidemics in the forties and fifties in the United States voiced new complaints.<sup>3,4</sup> Inventory studies demonstrated that the main symptoms were new or progressive muscle weakness, severe fatigue, and pain in muscles and joints.<sup>5-7</sup> Less common symptoms included muscle atrophy, difficulties with breathing and swallowing, sleep disorders, and cold intolerance. These symptoms were termed the postpoliomyelitis syndrome (PPS).<sup>8</sup> The diagnostic criteria for PPS have changed over time,<sup>9-11</sup> and the diagnosis of PPS is currently based on the general criteria presented in table 1.<sup>12</sup>

The prevalence of late onset neuromuscular symptoms varies between 29% and 75% in population-based studies of polio survivors.<sup>13-16</sup> This large variation depends on the methodological differences between studies with regard to the selection of the study populations, the definition of the symptoms, and the methods of assessment. In a population-based study that was carried out in 1995 to investigate 260 former victims of the 1956 polio outbreak in the Netherlands, 58% of the respondents reported that their muscle weakness had increased.<sup>17</sup> Since 1924, 14,682 cases<sup>a</sup> of poliomyelitis have been reported to the national health authorities in the Netherlands.

The course of PPS is slowly progressive, and the rate of decline in muscle strength is assumed to be slow. Studies with a follow-up of less than 4 years did not demonstrate any progression of muscle weakness,<sup>18-20</sup> but data from longer term studies indicate a decline in strength of approximately 1-2% per year.<sup>21,22</sup>

PPS negatively affects functioning in daily life. Growing restrictions in the ability to perform activities are mainly found for mobility-related activities such as walking, climbing stairs, and transfers.<sup>5,7,14,23-25</sup> Mobility problems affect the level of independence and also decrease life satisfaction.<sup>26</sup> The physical functioning of patients with PPS was found to decline over a 6-year period.<sup>27</sup> Over a period of 4-5 years, a significant increase in the degree of handicap with regard to mobility, occupation, and social integration was found in PPS subjects, while in non-PPS subjects the degree of handicap remained unchanged.<sup>28</sup>

**Table 1** Criteria for postpoliomyelitis syndrome

- 
- 1) Prior paralytic poliomyelitis with evidence of motor neuron loss, as confirmed by history of the acute paralytic illness, signs of residual weakness and atrophy of muscles on neurologic examination, and signs of denervation on electromyography
  - 2) A period of partial or complete functional recovery after acute paralytic poliomyelitis, followed by an interval (usually 15 years or more) of stable neurologic function
  - 3) Gradual or sudden onset of progressive and persistent new muscle weakness or abnormal muscle fatigability (decreased endurance), with or without generalized fatigue, muscle atrophy, or muscle and joint pain
  - 4) Symptoms persist for at least one year
  - 5) Exclusion of other neurologic, medical and orthopedic problems as causes of symptoms
- 

## Pathophysiology

Acute paralytic poliomyelitis develops in 0.1-2% of all infections when the polio virus invades the central nervous system and predominantly destructs the spinal motor neurons.<sup>1</sup> In severe cases, affection of the brain stem may result in death.

The acute stage of polio is followed by a period of neurological and functional recovery that may last for several months to years.<sup>1</sup> During this period, the affected

motor neurons that have survived the acute stage recover and regain their function. Denervated muscle fibres from permanently destroyed motor neurons are reinnervated through collateral sprouting from surviving axons, and motor units may increase five to eight times in size.<sup>29-32</sup> Strength also improves because of muscle fibre hypertrophy,<sup>33-35</sup> and fibre areas may increase up to twice the normal size.<sup>35</sup> It is assumed that muscle fibre hypertrophy develops in response to the relatively heavy load on paretic muscles in performing daily life activities.<sup>34</sup> At the end of the recovery period, a varying degree of residual paresis remains. This situation usually lasts for several decades, providing stable muscle strength and functioning.

The most widely accepted hypothesis for PPS was presented by Wiechers and Hubbell.<sup>36,37</sup> They assumed that the enlarged motor units would not remain stable throughout life, but degenerate prematurely due to persistent, high metabolic stress on the motor neurons. The degeneration of these motor units causes a slowly progressive loss of axonal sprouts. This concept has been confirmed through the finding of single atrophic muscle fibres in muscle biopsy studies.<sup>34,38,39</sup>

In addition, whole motor units may also collapse. In a prospective study estimating the number of motor units the rate of motor unit loss in prior poliomyelitis patients was twice the rate of motor unit loss in healthy subjects over 60 years of age.<sup>40</sup> However, a loss of entire motor units is not a common observation in muscle biopsy studies.<sup>34,39</sup> Moreover, muscle strength declines slowly over time.<sup>21,22</sup> Therefore, new muscle weakness in PPS is primarily the result of isolated degeneration of motor nerve terminals.

Jubelt and Cashman suggested that during an intervening period before degeneration, which may last for weeks to years, the terminal axons do not function properly, and complaints such as fatigue and lack of endurance may be due to dysfunction of terminal axons rather than degeneration.<sup>41</sup> Dysfunction of terminal axons was confirmed in stimulation single fibre electromyography (S-SFEMG) studies that found signs of neuromuscular transmission defects such as increased jitter and blockings.<sup>42,43</sup> It appeared that 10-20% of neuromuscular junctions in the symptomatic muscles of PPS patients were below the threshold for effective transmission. Trojan and Cashman discovered that jitter significantly increased at

high stimulation rates during S-SFEMG.<sup>44</sup> This finding suggests that the terminal axonal dysfunction is partly due to a defect in the release of the neurotransmitter acetylcholine.

Another factor that may contribute to new muscle weakness is an impaired ability to activate the muscles.<sup>45</sup> Impaired activation has been found significantly more often in prior polio patients with PPS than in prior polio patients with no new symptoms.<sup>46,47</sup> This may be due to the late impairment in motor unit functioning, or it may be the result of an impaired reflex drive.<sup>48</sup>

## Pharmacological treatment for PPS

Since there is no curative treatment for PPS, the management of PPS essentially aims to preserve the remaining muscle capacity and to prevent overloading of the symptomatic muscles. Multidisciplinary rehabilitation programmes usually consist of a combination of exercises, assistive devices, environmental adaptations, and changes in life-style. Several studies recommend non-fatiguing exercises to improve strength and endurance in patients with PPS.<sup>49-51</sup> Assistive devices, such as braces and crutches, may also be helpful to support weak muscles and to stabilize joints.<sup>52,53</sup> Changes in life style include the pacing of activities and the integration of rest intervals to relieve the symptoms.<sup>54</sup>

In addition to conservative treatment for PPS, a number of pharmacological agents have been tested (table 2). Human growth hormone<sup>55,56</sup> and insulin-like growth factor-1<sup>57</sup> were tested because they promote protein synthesis in muscle cells and axonal sprouting. Amantadine<sup>58</sup>, bromocriptine<sup>59</sup>, and selegiline<sup>60</sup> are three centrally acting dopaminergic agonists that were tested to diminish fatigue, and high-dose prednisone<sup>61</sup> was tested for its strong anti-inflammatory effect. Positive treatment effects were only found in studies with an open design or with a small sample size.<sup>55,59,60</sup> No medication has been proven to increase strength or decrease fatigue in patients with PPS in a randomised controlled trial.

**Table 2** Pharmacotherapy for postpoliomyelitis syndrome: recent trials

| Drug                                       | Category                   | Type of Trial                        | N  | Results in patients with PPS  |
|--|----------------------------|--------------------------------------|----|---|
| Human growth hormone <sup>55,56</sup>      | Hormone                    | Open trial                           | 5  | Little or no improvement in muscle strength   |
| Insulin-like growth factor-1 <sup>57</sup> | Growth factor              | Open trial                           | 11 | No improvement in muscle strength   |
|  |                            | Randomised, placebo-controlled trial | 22 | No improvement in muscle strength and fatigability, some improvement in recovery after exercise |
| Amantadine <sup>58</sup>                   | Anti-viral                 | Randomised, placebo-controlled trial | 23 | No significant decrease in fatigue  |
| Bromocriptine <sup>59</sup>                | Dopamine receptor agonist  | Placebo-controlled, cross-over trial | 5  | Decrease in fatigue symptoms in three patients  |
| Selegiline <sup>60</sup>                   | Neuro-protective agent     | Case studies                         | 2  | Decrease in PPS symptoms  |
| Prednisone (high-dose) <sup>61</sup>       | Steroid, anti-inflammatory | Randomised, placebo-controlled trial | 17 | No significant improvement in strength or decrease in fatigue                                   |

## Pyridostigmine

In the early nineties, Trojan and co-workers found that neuromuscular transmission defects in PPS patients could be ameliorated by injecting edrophonium (an anticholinesterase) into symptomatic muscles.<sup>62</sup> They also investigated oral use of the anticholinesterase Pyridostigmine (Mestinon), a drug used to treat muscle fatigability in myasthenia gravis.<sup>63</sup> Pyridostigmine inhibits the breakdown of acetylcholine by the enzyme cholinesterase, thereby prolonging the survival and effect of acetylcholine in the neuromuscular junction. Pyridostigmine may directly decrease fatigue and increase strength by restoring effective transmission in blocked or defective neuromuscular junctions.<sup>62,64</sup> In the longer term, pyridostigmine may increase strength by promoting secretion of the human growth hormone and, consequently, trophic growth factors such as insulin-like growth factor-1.<sup>65</sup>

Two open trials of pyridostigmine demonstrated a decline in fatigue, and reported a significant relationship between the decline in fatigue and the improvement in neuromuscular transmission.<sup>62,66</sup> In a placebo-controlled cross-over trial (published as an abstract) a mild improvement in the strength of weak muscles was found.<sup>67</sup>

In 1999, the results of the North American postpoliomyelitis pyridostigmine study were published by Trojan and co-workers.<sup>68</sup> This was a randomised, double-blind, placebo-controlled multicenter trial in 126 PPS patients. It was found that 180 mg pyridostigmine per day for a period of 6 months had no effect on physical functioning (measured with the Short Form Health Survey-36), muscle strength (measured with the Tufts Quantitative Neuromuscular Examination) or fatigue (measured with the Fatigue Severity Scale and the Hare Fatigue Symptom Scale). The negative results of this multicenter trial may imply that pyridostigmine is not effective in the treatment of PPS. On the other hand, the negative results may also be due to methodological limitations of the study design with respect to patient selection, outcome measures and the dosage of pyridostigmine.<sup>69</sup>

## Purpose of this thesis

Given the limitations of the North American postpoliomyelitis pyridostigmine study, a randomised controlled trial (RCT) is carried out, which includes detailed

measurements and a higher dosage of pyridostigmine for selected patients with PPS. The results of this study are reported in this thesis.<sup>70</sup> PPS patients with severe fatigue and with neuromuscular transmission defects, as demonstrated by S-SFEMG, are included in the study, because they are expected to benefit most from pyridostigmine.

The outcome measures are chosen at the levels of perceived health, physical performance, and muscle function. This makes it possible to investigate the effectiveness of the treatment on different levels of functioning, as well as the relationships between the effects on these different levels. The primary outcome is fatigue, measured with the Nottingham Health Profile,<sup>71</sup> a validated and widely accepted health-related quality of life scale that has been used in several studies of PPS patients.<sup>25,72,73</sup> The Nottingham Health Profile was found to be responsive in an RCT with fibromyalgia patients.<sup>74</sup> Secondary outcomes include measurements of physical performance, such as timed walking tests and walking activity in the daily environment, and measurements of muscle function, such as muscle strength, muscle fatigability, and maximal voluntary muscle activation. During the medication period neuromuscular transmission is investigated to assess the pharmacological effectiveness of 60 mg of pyridostigmine 4 times per day, which is 60 mg per day higher than the dosage prescribed in the North American postpoliomyelitis pyridostigmine study.

A further aim of this thesis is to investigate the validity and reproducibility of the main outcome measures used in the trial to measure fatigue, walking performance, and muscle strength. The outcome measures should measure the symptom of interest reliably, and should also be sensitive enough to identify clinically relevant changes.

## **Outline of this thesis**

This thesis describes the results of a randomised, double-blind, placebo-controlled trial investigating the effect of pyridostigmine on fatigue, physical performance and muscle function in patients with PPS, and focuses on the validity and reproducibility of the main outcome measures used in this trial.



**Chapter 2** contains detailed comments on the results of the North American postpoliomyelitis pyridostigmine study carried out by Trojan and colleagues, and introduces the plan to set up a new trial.

**Chapter 3** investigates the validity and reproducibility of four questionnaires that have recently been used to determine the severity of fatigue in patients with PPS: the Fatigue Severity Scale; the energy category of the Nottingham Health Profile; the Fatigue item of the Polio Problem List; and the Short Fatigue Questionnaire. Concurrent and construct validity (Mokken scale analysis) are investigated, and the ability to detect change is assessed, as well as the effect of sample size on the ability to detect change.

**Chapter 4** investigates the reproducibility of measurements of maximal strength and maximal voluntary activation of symptomatic quadriceps muscles, using a fixed dynamometer. Variability in voluntary activation may contribute to the variability in muscle performance. Therefore, the association between variability in strength and voluntary activation is determined.

In **Chapter 5**, the reproducibility of walking performance and physical effort is determined in two walking tests: one at self-preferred speed and one at maximal speed. Physical effort is measured by means of heart rate and the patient's rating of perceived exertion (Borg scale). The association between the variability in walking performance and the variability in physical effort is investigated, and the appropriateness of perceived exertion for monitoring and pacing activities is discussed.

**Chapter 6** describes the results of the randomised, double-blind, placebo-controlled trial of pyridostigmine in 67 patients with PPS who have an increased level of fatigue and demonstrated neuromuscular transmission defects in a symptomatic quadriceps muscle. The primary outcome is perceived fatigue, measured with the energy category of the Nottingham Health Profile. Secondary objectives are to investigate the effects on physical performance and muscle function.

**Chapter 7** investigates whether walking in a clinical setting reflects effort levels and characteristics such as step cadence and speed of normal walking in daily life. In addition, relationships are determined between walking test performance, the amount of walking in daily life, and perceived physical mobility problems.

**Chapter 8** discusses the results of the randomised controlled trial and the appropriateness of the main outcome measures used in the trial. Suggestions are made for the treatment of, and the evaluation of treatment effects in patients with PPS in the future.

<sup>a</sup> Data provided by J.K. van Wijngaarden, MD; Inspectorate for Health Care of the Ministry of Health, The Hague, The Netherlands.

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## CHAPTER 2



Comments on the North American  
postpoliomyelitis pyridostigmine study

Letter to the editor

Frans Nollet, Herwin Horemans and Anita Beelen

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No substantial beneficial effect of pyridostigmine in patients with postpoliomyelitis syndrome (PPS) was found by Trojan et al.<sup>1</sup> This negative result is disappointing, because its potential benefit has been shown in previous studies,<sup>2,3</sup> and fatigue and walking difficulties are major problems in PPS.<sup>4</sup>

Although the trial was a well designed, double-blind study, its weakness seems primarily to be the lack of responsiveness of the outcome measures. These measures were probably chosen for pragmatic reasons, as the measurements had to be carried out at different sites. A multicenter design has the advantage of collecting enough patients to achieve sufficient statistical power within an acceptable time-frame. Unfortunately, this probably accounts for the negative results that, for most outcome measures, might have been foreseeable. The lack of responsiveness of the short form health survey-36 (SF-36), as discussed by the authors, has been confirmed in the evaluation of a rehabilitation treatment program in patients with MS.<sup>5</sup> The SF-36 probably only detects large changes; for instance, in patients who deteriorate rapidly.<sup>6</sup> Although correlation coefficients of reproducibility for the fatigue scales were high, they give no information about the ability to detect change.<sup>7</sup>

At best, pyridostigmine could be expected to cause relatively small changes in strength. The fact that the average pretrial intra-rater differences for the Tufts Quantitative Neuromuscular Examination measurements were below 10% provides no information about the smallest mean difference that could be detected without mentioning the standard error. Presenting changes in strength as a percentage change from baseline values amplifies changes in weak muscles tremendously. For instance, with a strength of 10N, an increase of 5N represents a 50% change, whereas the same increase at 100N would imply only a 5% change. Table 3<sup>1</sup> shows that the percentage change in strength decreases with increasing relative strength. Thus, the nonsignificant change of 41.8% in very weak muscles may seem large, but is in fact very small in Newtons.

The study illustrates that the step from open, sophisticated, electrophysiologic studies to a multicenter trial with global outcome measures may be too big. If the results are negative, considerable thought should be given to the possible shortcomings of the study. Although criticizing in retrospect is relatively easy, it may have been better to

first study the effect of pyridostigmine in a double-blind trial in a homogeneous group of patients, all who exceed a predefined level of fatigue and who demonstrate transmission defects in a symptomatic muscle group that is functionally important, and in which strength can be measured reliably.

In April 1999 we started such a study, which involves a fatigue protocol, functional performance tests, and electromyography of motor-unit remodeling, which may be an important effect modifier. If the results in selected patients are positive, the next step would be to investigate the generalisability. As stated by Dalakas,<sup>8</sup> exercise and reassurance are important measures, but the bottom-line of treatment for PPS is still the pacing of activities. In the near future we hope to respond to the final remarks of Trojan et al.<sup>1</sup> Excluding pyridostigmine as a possible beneficial treatment for PPS patients seems, at present, to be too premature.

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## CHAPTER 3

### A comparison of 4 questionnaires to measure fatigue in postpoliomyelitis syndrome

Herwin Horemans, Frans Nollet, Anita Beelen  
and Gustaaf Lankhorst

*Arch Phys Med Rehabil 2004; 85: 392-398*



## ABSTRACT

**Objective:** To assess the comparability and reproducibility of 4 questionnaires used to measure fatigue in postpoliomyelitis syndrome (PPS).

**Design:** Repeated-measures at a 3-week interval.

**Setting:** University hospital.

**Participants:** Convenience sample of 65 patients with PPS.

**Interventions:** Not applicable.

**Main outcome measures:** The Fatigue Severity Scale (FSS), the Nottingham Health Profile (NHP) energy category, the Polio Problem List (PPL) fatigue item, and the Dutch Short Fatigue Questionnaire (SFQ).

**Results:** Correlations of scores between questionnaires were all significant ( $P<.01$ ) and ranged from .43 (between the NHP energy category and the PPL fatigue item) to .68 (between the PPL fatigue item and the SFQ). Scores on the second visit, normalised to a 0 to 100 scale, were: FSS,  $78\pm15$ ; NHP energy category,  $47\pm35$ ; PPL fatigue item,  $81\pm17$ ; and SFQ,  $65\pm22$ . Except for the difference between the FSS and the PPL fatigue item, the differences in scores between the questionnaires were significant ( $P<.01$ ). Scale analysis indicated that all questionnaires measured the same unidimensional construct. The reproducibility of the FSS, the PPL fatigue item, and the SFQ was moderate. The smallest detectable change was 1.5 points for the FSS, and 2 points for the PPL fatigue item and the SFQ.

**Conclusions:** Although the questionnaires measure the same fatigue construct in PPS, the results are not interchangeable because the ranges of measurement differ. The NHP energy category, in particular, appeared to have a high detection threshold. The moderate reproducibility of the questionnaires indicates a lack of precision, especially when applied at the individual patient level.

One of the major problems in postpoliomyelitis syndrome (PPS) is fatigue.<sup>1,2</sup> Approximately 66% to 89% of patients with PPS perceive symptoms of increased fatigue,<sup>3-5</sup> which may lead to a decline in their physical activities<sup>6,7</sup> and social functioning.<sup>1,8</sup> In studies in which the severity of fatigue in PPS was measured, different group scores have been reported.<sup>2,6,7,9-13</sup> However, fatigue was assessed with different questionnaires. Comparing results obtained with different questionnaires in the various studies is problematic, because it is not known whether the differences in scores reflect differences in the severity of fatigue between the study populations or differences in the response characteristics of the questionnaires. Items may differ in the range for which they measure the severity of fatigue. Furthermore, items may assess different aspects of fatigue—for example, some items measure fatigue associated with exertion and other items measure the perception of fatigue.<sup>14</sup> Therefore, differences in the construct of fatigue may be present both within and between the questionnaires.

Because fatigue has been used as an outcome measure, both in the treatment<sup>15-18</sup> and prospective follow-up studies of PPS,<sup>19</sup> another important aspect that needs to be addressed is whether questionnaires that measure fatigue are reliable and sensitive enough to detect change.<sup>20</sup>

Our study was undertaken to investigate the comparability and reproducibility of 4 questionnaires that have been used to assess the severity of fatigue in PPS: the Fatigue Severity Scale (FSS), the energy category of the Nottingham Health Profile (NHP), the fatigue item on the Polio Problem List (PPL), and the Short Fatigue Questionnaire (SFQ). The comparability of the 4 questionnaires was investigated by determining their concurrent and construct validity. The reproducibility of the FSS, the PPL fatigue item, and the SFQ was investigated by determining the test-retest reliability and the smallest detectable change.

## METHODS

### Study population

Sixty-five patients with PPS were recruited from the Dutch Neuromuscular Diseases Association (Vereniging Spierziekten Nederland), (academic) hospitals, and rehabilitation centers. All patients met the following inclusion criteria: (1) PPS, according to the Halstead criteria,<sup>21</sup> that is, a history of paralytic polio, a period of neurologic recovery followed by an interval of functional stability of at least 15 years, and the onset of weakness in previously affected and/or unaffected muscles not due to inactivity, possibly accompanied by excessive fatigue, muscle pain, decreased endurance, and atrophy; (2) symptoms of increased fatigue, that is, a minimum score of 10 on the SFQ, which is above the normal values in a healthy Dutch population; (3) age 18 to 70 years; and (4) no other diseases that could cause the symptoms. The patients underwent a medical examination to check the criteria, and all participants gave written informed consent.

### Questionnaires

*Fatigue Severity Scale.* The FSS consists of 9 statements that are scored on a 7-point Likert scale, ranging from 1 (strongly disagree) to 7 (strongly agree). For each subject, a total score is calculated as the mean score of the 9 statements. A lower total score indicates less effect of fatigue on everyday life. The FSS has shown good internal consistency (Cronbach  $\alpha$  range, .81-.95)<sup>22-24</sup> and test-retest reliability in patients with multiple sclerosis or systemic lupus erythematosus (Pearson  $r=.84$ ),<sup>22</sup> immune-mediated polyneuropathies (intraclass correlation coefficient [ICC]=.86),<sup>23</sup> and chronic hepatitis C (ICC=.82).<sup>24</sup>

*Nottingham Health Profile.* The NHP energy category is 1 of the 6 categories of the NHP and consists of 3 yes-no questions. The category score is calculated by dividing the number of questions answered with yes by the total number of questions and multiplied by 100, which results in a score ranging from 0 (no complaints) to 100 (answered yes to all questions). The Dutch version of the NHP energy category has shown satisfactory internal consistency (Cronbach  $\alpha=.77$ )<sup>25</sup> and test-retest reliability

(Spearman  $\rho$  range, .77-.86) in patients with chronic heart failure and myocardial infarction or stroke.<sup>25,26</sup>

*Polio Problem List.* The PPL fatigue item is 1 of the 16 items on the PPL.<sup>2</sup> The PPL fatigue item assesses the extent to which fatigue is perceived as a problem, and it is scored on an 8-point Likert scale, ranging from 0 (no problem) to 7 (severe problem).

*Short Fatigue Questionnaire.* The SFQ consists of 4 statements that are scored on a 7-point Likert scale, similar to the scale of the FSS. For each subject, a total score is calculated as the mean score of the 4 statements. The SFQ has shown good internal consistency (Cronbach  $\alpha$ =.88) and was found able to discriminate between patients and healthy subjects.<sup>27</sup>

### Assessment protocol

Two study visits to the hospital were scheduled on the same day of the week and at the same time, with a 3-week interval. The questionnaires were administered once on each study visit, except for the NHP, which was administered only on the second occasion. Before each visit, the patients received brief instructions on how to complete each questionnaire. They were asked to score only for the previous 2 weeks. The subjects were seated in a quiet room and were allowed to take all the time they needed to fill in the questionnaires and to rest in between, if necessary. In general, the time needed to fill in the questionnaires was less than 15 minutes. On both visits, the questionnaires were administered in the same order.

### Data analysis

Validity was assessed on the basis of data obtained during the second study visit.

*Concurrent validity.* Correlations between the scores of the different questionnaires were determined by calculating the Spearman rank correlation coefficients. To determine whether there were any systematic differences between the scores of the questionnaires, the normalised scores of the questionnaires (on a 0-100 scale) were compared, using the Friedman analysis of variance (ANOVA). Post hoc (pairwise) comparisons were made, using Wilcoxon signed-rank tests corrected for multiple testing ( $\alpha$ =.05/6, with 6 pairs tested).<sup>28</sup>

*Construct validity.* To investigate the construct validity of the questionnaires, a Mokken scale analysis for polytomous items<sup>a</sup> was performed to determine the single scale homogeneity of the 17 items of the 4 questionnaires.<sup>29</sup> Mokken scale analysis is a nonparametric approach to the item response theory.<sup>30</sup> The concept of homogeneity refers to the Mokken model of monotone homogeneity, which assumes that the items measure the same construct, that item and item-step scores are locally independent, and that the item and the item-step response functions are monotonely nondecreasing functions of the latent trait.<sup>29</sup> The Loevinger *H* scalability coefficient gives an indication of the extent to which the set of items form a homogeneous scale. An *H* smaller than .30 indicates a nonhomogeneous scale; between .30 and .40, weak homogeneity; between .40 and .50, moderate homogeneity; and greater than .50, strong homogeneity.<sup>29</sup> The stronger the homogeneity, the more all items measure the same construct and the better the items discriminate between individual different positions on the construct. Homogeneous scales are considered to be unidimensional. Unlike dichotomous items, it is not possible to place polytomous items in hierarchic order with respect to the latent trait, because the order depends on both the item response functions and the item-step response functions.

*Reproducibility.* Systematic differences between the 2 study visits were investigated for the total scores of the FSS and the SFQ using *t* tests and for the PPL fatigue item and item scores of the FSS and the SFQ using Wilcoxon signed-rank tests. The distribution of the FSS and SFQ scores was considered normal. The test-retest reliability of the FSS and the SFQ was assessed with ICCs and the 95% confidence intervals (CIs) of the ICCs, using a random-effects 1-way ANOVA.<sup>31</sup> Test-retest reliability of the PPL fatigue item was analyzed by calculating the Spearman correlation coefficient. The internal consistency of the FSS, the NHP energy category, and the SFQ on the 2 study visits was determined with the Cronbach  $\alpha$  coefficient. An  $\alpha$  coefficient of .70 is considered sufficient, and an  $\alpha$  coefficient of more than .80 is considered good for the purpose of group comparisons.<sup>32</sup>

Test-retest reliability for the 3 questionnaires was also assessed by means of Bland-Altman plots, in which for each subject the difference between the scores of the 2 visits was plotted against the mean of these 2 scores.<sup>33</sup> The 95% limits of agreement (mean difference  $\pm$  2 standard deviations [SDs]) were calculated for each

questionnaire to assess the smallest detectable change, which gives an indication of the change that is needed to detect a real change, taking chance variation or measurement error into account.<sup>34</sup> A questionnaire is able to detect an individual change in score if the change lies outside the limits of agreement.

For comparison of a group score in a paired situation, the smallest detectable change depends on the sample size. The effect of sample size on the smallest detectable change was estimated from  $n > k \cdot \sigma^2 / \Delta^2$ , with  $n$  being the number of subjects,  $k$  the constant based on tables of standard normal curve ( $k=10.51$  for  $\alpha=.05$  and  $\beta=.10$ ),  $\sigma^2$  the variance of differences, and  $\Delta$  the smallest detectable change.<sup>35</sup> Statistical analysis was performed with the SPSS, version 10.0.5, statistical software package.<sup>b</sup> An  $\alpha$  level of  $P$  less than .05 was used for all tests of significance.

## RESULTS

Sixty-five patients (42 women, 23 men) with a mean age of  $52 \pm 8$  years completed the questionnaires on both visits. The mean time since the onset of polio was  $49 \pm 8$  years, and the mean time since new neuromuscular symptoms were perceived was  $10 \pm 6$  years. The total score and the item scores of the questionnaires on the first and second study visits are presented in table 1. The highest item scores on the FSS were found on the second visit for items 6 ("My fatigue prevents sustained physical functioning"; score,  $6.3 \pm 1.0$ ) and 8 ("Fatigue is among my three most disabling symptoms"; score,  $6.2 \pm 1.3$ ). The highest scores on the NHP energy category were found for items 1 ("I'm tired all the time"; score,  $58 \pm 50$ ) and 3 ("I soon run out of energy"; score,  $62 \pm 49$ ). The highest score on the SFQ was found on the first visit for item 2 ("I tire easily"; score,  $5.9 \pm 1.3$ ).

### Concurrent validity

Pairs of total scores of questionnaires correlated significantly ( $P < .01$ ), with the highest correlation coefficient of .68 between the PPL fatigue item and the SFQ and the lowest correlation coefficient of .43 between the NHP energy category and the PPL fatigue item (table 2).

**Table 1** Total and item scores on the first and second study visits

|   | First visit    | Second visit   | <i>P</i> value |
|---|----------------|----------------|----------------|
| <i>FSS (range, 1-7)</i>   | <i>5.4±1.1</i> | <i>5.7±0.9</i> | <i>.03</i>     |
| 1. My motivation is lower when I am fatigued                                | 5.0±1.9        | 5.3±1.8        | .22            |
| 2. Exercise brings on my fatigue  | 5.8±1.5        | 5.8±1.3        | .93            |
| 3. I am easily fatigued   | 5.6±1.6        | 5.9±1.3        | .02            |
| 4. Fatigue interferes with my physical functioning                          | 5.7±1.6        | 5.9±1.1        | .15            |
| 5. Fatigue causes frequent problems for me                                  | 4.4±1.7        | 4.9±1.7        | .03            |
| 6. My fatigue prevents sustained physical functioning                       | 5.9±1.7        | 6.3±1.0        | .10            |
| 7. Fatigue interferes with carrying out certain duties and responsibilities | 5.3±1.7        | 5.5±1.5        | .40            |
| 8. Fatigue is among my three most disabling symptoms                        | 6.1±1.4        | 6.2±1.3        | .56            |
| 9. Fatigue interferes with my work, family, or social life                  | 5.3±1.7        | 5.2±1.8        | .43            |
| <i>NHP energy category (range, 0-100)</i>                                   |                | <i>47±35</i>   |                |
| 1. I'm tired all the time   |                | 58±50          |                |
| 2. Everything is an effort  |                | 22±41          |                |
| 3. I soon run out of energy   |                | 62±49          |                |
| <i>PPL fatigue item (range, 0-7)</i>  | <i>5.5±1.4</i> | <i>5.7±1.2</i> | <i>.05</i>     |
| <i>SFQ (range, 1-7)</i>   | <i>5.0±1.2</i> | <i>4.9±1.3</i> | <i>.72</i>     |
| 1. I feel tired   | 4.9±1.5        | 4.9±1.7        | .90            |
| 2. I tire easily  | 5.9±1.3        | 5.8±1.5        | .12            |
| 3. I feel fit   | 5.0±1.6        | 5.1±1.6        | .43            |
| 4. I feel physically exhausted  | 4.0±1.9        | 3.9±1.9        | .57            |

Values are mean ± SD. Differences between study visits were investigated for the total scores of the FSS and the SFQ using *t* tests, and for the PPL fatigue item and item scores of the FSS and the SFQ using Wilcoxon signed-rank tests.

The normalised total and item scores of the questionnaires on the second study visit are given in table 3, and the normalised total scores are also presented in boxplots (figure 1). The mean normalised total scores were highest for the PPL fatigue item ( $81 \pm 17$ ) and lowest for the NHP energy category ( $47 \pm 35$ ). The mean normalised total scores for the FSS were  $78 \pm 15$ , and for the SFQ they were  $65 \pm 22$ . The normalised total scores of the questionnaires differed significantly (Friedman test,  $P < .01$ ). Pairwise comparisons of the total scores of the questionnaires showed differences for all pairs of questionnaires ( $P < .05$ ), except for the FSS-PPL fatigue item pair.

**Table 2** Spearman correlation coefficients

|                     | FSS   | NHP energy<br>category | PPL fatigue<br>item | SFQ  |
|---------------------|-------|------------------------|---------------------|------|
| FSS                 | 1.00  |                        |                     |      |
| NHP energy category | 0.50* | 1.00                   |                     |      |
| PPL fatigue item    | 0.60* | 0.43*                  | 1.00                |      |
| SFQ                 | 0.47* | 0.67*                  | 0.68*               | 1.00 |

\*Significant correlation ( $P < .01$ ).

### Construct validity

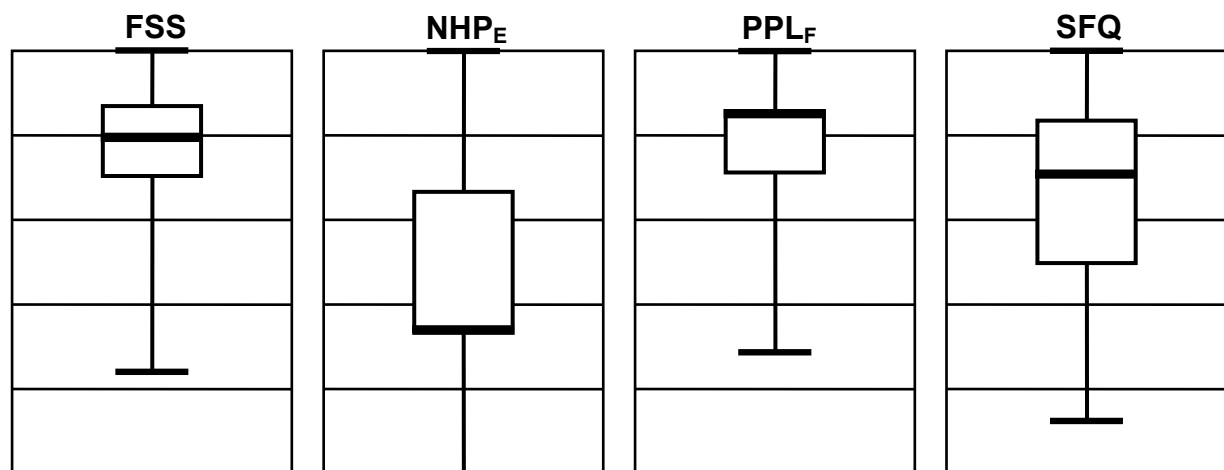
Scale analysis performed on the 17 items of the 4 questionnaires showed that 15 of the 17 items formed a unidimensional scale ( $H = .49$ ). The first 2 items of the FSS did not fit into this scale and did not form a separate scale ( $H = -.11$ ). When scale analysis was performed on the FSS as a separate scale, once again the first 2 items misfitted. The item  $H$  for item 1 (“My motivation is lower when I am fatigued”) was .05, and the item  $H$  for item 2 (“Exercise brings on my fatigue”) was  $-.05$ . Scale analysis on the remaining 7 items of the FSS showed  $H$  equal to .63.



**Table 3** Normalised total and item scores (range, 0-100) on the second study visit

|   | Mean±SD      | 25        | 50        | 75        |
|---|--------------|-----------|-----------|-----------|
| <i>FSS</i>  | <i>78±15</i> | <i>70</i> | <i>80</i> | <i>88</i> |
| 1. My motivation is lower when I am fatigued                                | 71±30        | 67        | 83        | 100       |
| 2. Exercise brings on my fatigue  | 79±22        | 75        | 83        | 100       |
| 3. I am easily fatigued   | 82±22        | 75        | 83        | 100       |
| 4. Fatigue interferes with my physical functioning                          | 82±18        | 67        | 83        | 100       |
| 5. Fatigue causes frequent problems for me                                  | 64±28        | 50        | 67        | 83        |
| 6. My fatigue prevents sustained physical functioning                       | 88±17        | 83        | 100       | 100       |
| 7. Fatigue interferes with carrying out certain duties and responsibilities | 74±25        | 67        | 83        | 100       |
| 8. Fatigue is among my three most disabling symptoms                        | 87±21        | 83        | 100       | 100       |
| 9. Fatigue interferes with my work, family, or social life                  | 69±30        | 50        | 83        | 100       |
| <i>NHP energy category</i>  | <i>47±35</i> | <i>33</i> | <i>33</i> | <i>67</i> |
| 1. I'm tired all the time   | 58±50        | 0         | 100       | 100       |
| 2. Everything is an effort  | 22±41        | 0         | 0         | 0         |
| 3. I soon run out of energy   | 62±49        | 0         | 100       | 100       |
| <i>PPL fatigue item</i>   | <i>81±17</i> | <i>71</i> | <i>86</i> | <i>93</i> |
| <i>SFQ</i>  | <i>65±22</i> | <i>50</i> | <i>71</i> | <i>83</i> |
| 1. I feel tired   | 65±28        | 50        | 67        | 83        |
| 2. I tire easily  | 79±25        | 67        | 83        | 100       |
| 3. I feel fit   | 68±27        | 50        | 67        | 83        |
| 4. I feel physically exhausted  | 48±32        | 17        | 50        | 83        |

Total and item scores are mean ± SD and quartiles.



**Figure 1** Boxplots of normalised total scores (scale range, 0-100) on the second study visit. The box represents the interquartile range with the bold line as median value. The whiskers represent the range of the scores. Abbreviations: NHP<sub>E</sub>, NHP energy category; PPL<sub>F</sub>, PPL fatigue item.

### Reproducibility

The total score of the FSS was higher on the second study visit than on the first (mean difference,  $0.2 \pm 0.8$ ;  $P = .03$ ) (table 1). The score increased significantly for items 3 (“I am easily fatigued”;  $P = .02$ ) and 5 (“Fatigue causes frequent problems for me”;  $P = .03$ ). The total and item scores of the PPL fatigue item and the SFQ did not differ on retest. The ICCs (95% CI) for the FSS and the SFQ were .83 (.72-.90) and .84 (.73-.90), respectively. The Spearman  $\rho$  for the PPL fatigue item was .80 ( $P < .01$ ).

The FSS showed good internal consistency on the 2 study visits (Cronbach  $\alpha = .85$  and .80, respectively). The internal consistency of the NHP energy category on the second study visit (Cronbach  $\alpha = .59$ ) was below the .70 standard recommended for group comparisons.<sup>32</sup> The SFQ showed reasonable internal consistency on both study visits (Cronbach  $\alpha = .79$  and .77, respectively).

The mean of the individual scores on the 2 study visits was plotted against the difference of the scores on both visits for the FSS, the PPL fatigue item, and the SFQ (figure 2). The 95% limits of agreement, when expressed as a percentage of the mean of 2 study visits, were narrowest for the FSS and widest for the SFQ (table 4). The effect of sample size on the smallest detectable change is presented in table 5.

For comparison of a group score in a paired situation, changes of less than 10% on the FSS, the PPL fatigue item, and the SFQ were required for sample sizes of at least 50 subjects.

**Table 4** Limits of agreement

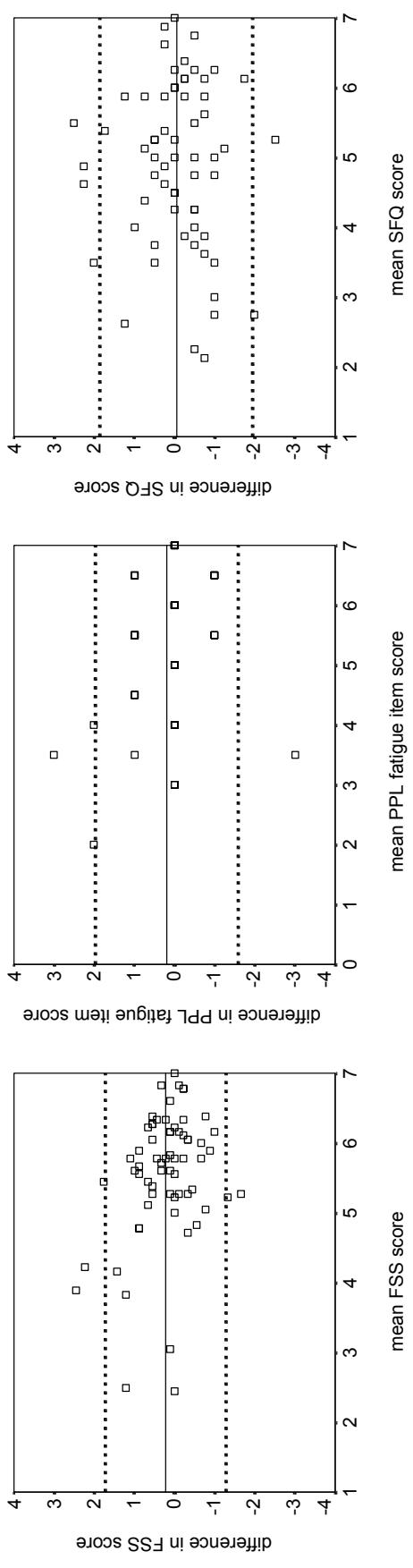
|                                  | Mean of scores<br>of the 2 study visits | Difference in scores<br>of the 2 study visits | 95% Limits of agreement   |
|----------------------------------|---|---|---------------------------|
| FSS (range, 1-7)                 | 5.6±0.9                                 | 0.2±0.8                                       | -1.3 to 1.7 (-23% to 31%) |
| PPL fatigue item<br>(range, 0-7) | 5.6±1.2                                 | 0.2±0.9                                       | -2.0 to 2.0 (-36% to 36%) |
| SFQ (range 1-7)                  | 4.9±1.2                                 | -0.0±1.0                                      | -2.0 to 1.9 (-40% to 38%) |

The mean of the scores and the difference in scores of the 2 study visits are mean  $\pm$  SD. The difference is calculated as scores on the second study visit minus scores on the first study visit. The 95% limits of agreement are calculated as mean difference  $\pm 2$  SDs of the difference and are expressed in original scale points and as a percentage of the mean of the 2 study visits.

## DISCUSSION

Different questionnaires have been used to assess the severity of fatigue in PPS. However, little is known about the comparability and reproducibility of their results. In our study, both the validity and the reproducibility of various fatigue questionnaires were assessed in 65 patients with PPS. The data on reproducibility also provided information about the smallest detectable change for each questionnaire.

Although the PPS patients selected for our study had elevated levels of fatigue, the scores for fatigue measured with the FSS, the NHP energy category, and the PPL fatigue item were comparable to those reported in the literature.<sup>2,6,7,9-13,36</sup> It must be mentioned that most of the NHP energy category scores reported in the literature were calculated from weighted item scores.<sup>37</sup> However, the importance of weighting is under discussion,<sup>38,39</sup> and the median score of 33 found in our study is well within the range of values reported in the literature.<sup>2,11-13,36</sup>



**Figure 2** Bland-Altman plots for the FSS, the PPL fatigue item, and the SFQ. The difference is calculated as the score on the second study visit minus the score on the first study visit. The solid line represents the mean difference. The dotted lines represent the 95% limits of agreement.

**Table 5** The effect of sample size on the smallest detectable change

|                               | Individual | n=25      | n=50     |
|-------------------------------|------------|-----------|----------|
| FSS (range, 1-7)              | 1.5 (27%)  | 0.5 (9%)  | 0.3 (6%) |
| PPL fatigue item (range, 0-7) | 2.0 (36%)  | 0.6 (10%) | 0.4 (7%) |
| SFQ (range, 1-7)              | 1.9 (39%)  | 0.6 (13%) | 0.4 (9%) |

The smallest detectable change is expressed in original scale points and as a percentage of the mean of the 2 study visits. For an individual case, the change required will be approximately 2 SDs of the mean difference. For comparison of a group score in a paired situation, the smallest detectable change was calculated from the formula:  $n > k \cdot \sigma^2 / \Delta^2$ , where n=number of subjects, k=constant based on tables of standard normal curve ( $k=10.51$  for  $\alpha=0.05$  and  $\beta=0.10$ ),  $\sigma^2$ =variance of differences, and  $\Delta$ =smallest detectable change.<sup>35</sup>

## Validity

Analysis of concurrent validity showed low correlations (range, .43-.68) between the total scores of all pairs of questionnaires, which indicate that little of the variation in score of one questionnaire was explained by the variation in score of another questionnaire. Moreover, it was found that the normalised total scores differed between most questionnaires. Compared with the scores of the FSS, the PPL fatigue item, and the SFQ, the scores of the NHP energy category were markedly lower. It is well known that the dichotomous items of the NHP have a high threshold for positive scores<sup>40-42</sup> and are not likely to detect minor illnesses.<sup>43</sup> Especially item 2 of the NHP energy category ("Everything is an effort"), which was scored affirmative by only 22% of the patients (table 1), showed a considerable ceiling effect.

In contrast with the NHP energy category, the FSS and the PPL fatigue item seemed to have a low threshold. According to the median item values, 50% of the patients had a maximum score of 7 on the FSS for the items 6 ("My fatigue prevents sustained physical functioning") and 8 ("Fatigue is among my three most disabling symptoms"). Therefore, item 2 of the NHP energy category and items 6 and 8 of the FSS may assess different aspects of fatigue. However, it appeared that 15 of the 17 items on the 4 questionnaires formed an almost strongly homogeneous scale

( $H=.49$ ), which indicates that the questionnaires did not measure different constructs or other aspects of fatigue. Interestingly, the first 2 items of the FSS (“My motivation is lower when I am fatigued”; “Exercise brings on my fatigue”) did not fit in the overall scale, nor did they fit in their own 9-item FSS scale. The latter was surprising, because all 9 items of the FSS fit the assumption of unidimensionality when used to assess patients with chronic hepatitis C.<sup>24</sup> The fitting of these items may depend on the study population in which the FSS was applied. However, it must be stated that also in chronic hepatitis C patients,<sup>24</sup> the first 2 items of the FSS showed the lowest item-total correlations, which indicates that their scores reflected the total score least accurately.

### Reproducibility

The ICCs of the FSS (.83) and the SFQ (.84) and the Spearman  $\rho$  of the PPL fatigue item (.80) seemed to be satisfactory. The ICC of the FSS was in accordance with ICCs found in other groups of patients (ICC range, .82-.86).<sup>23,24</sup> However, the lower limits of the 95% CIs of the ICCs of the FSS (.72) and the SFQ (.73) found in this study suggest only moderate test-retest reliability.<sup>44,45</sup> This might be due to large day-to-day variations in fatigue in PPS patients. However, because the literature presents no data on the CIs of the ICCs for the FSS, the PPL fatigue item, or the SFQ in PPS patients, this cannot be verified. In addition, the moderate test-retest reliability of fatigue as an outcome measure may be inherent in its subjective character, because the perception of fatigue depends not only on physical but also mental and emotional status.<sup>46</sup>

The Cronbach  $\alpha$  values for internal consistency that were found for the FSS and for the NHP energy category were comparable to those reported in other studies.<sup>22-24,40,47,48</sup> With only 3 dichotomous items, the low internal consistency of the NHP energy category was not expected to be higher than already reported in other patient groups. The internal consistency of the SFQ was acceptable but lower than reported by Alberts et al.<sup>27</sup>

In addition to the assessment of reproducibility at the group level, it is also important to determine the reproducibility of an instrument at the individual level.<sup>49</sup> The limits of agreement found for the FSS, the PPL fatigue item, and the SFQ were

wide (table 4) and may indicate large individual day-to-day variations. With a 95% CI, the change in score of an individual, compared with the score on the first study visit, had to be at least 2 points on the scale of each questionnaire to be detected. The smallest detectable changes for the FSS, the PPL fatigue item, and the SFQ ranged from 27% to 39% (table 5). Therefore, at the individual level, the FSS, the PPL fatigue item, and the SFQ show too much variation in score to be able to detect changes in fatigue.

Although less appropriate for detecting differences within an individual, the FSS, the PPL fatigue item, and the SFQ may be useful for group comparisons, in which the smallest detectable changes are much smaller. In a sample size of 50, the FSS, the PPL fatigue item, and the SFQ can detect changes of less than 10% from baseline. Similar conclusions with respect to the ability to detect change have been reported for the NHP energy category.<sup>42,50</sup>

## CONCLUSIONS

When comparing the severity of fatigue in PPS reported in various studies, one should take into account the fact that, although the FSS, NHP energy category, PPL fatigue item, and SFQ measure the same construct of fatigue, the severity of fatigue may differ considerably as a result of differences in the range for which questionnaires measure fatigue. The NHP energy category, in particular, appeared to have a high detection threshold to measure fatigue.

The choice of the appropriate questionnaire to measure fatigue in PPS may depend on the expected range in the severity of fatigue and the desired responsiveness of the questionnaire. For instance, if one is only interested in identifying high levels of fatigue, the NHP energy category may be preferred. On the other hand, if the main interest is to identify changes in fatigue, for instance due to intervention, it should be realized that no differences between the FSS, the PPL fatigue item, and the SFQ were found for reproducibility, which was comparable for all questionnaires—that is, sufficient at the group level but lacking precision at the individual patient level. The choice may further depend on the desired simplicity of the instrument, that is, the number of questions. Finally, when applying the FSS to

measure fatigue in PPS, one should consider omitting items 1 and 2, because they do not appear to fit in the same fatigue construct as the other FSS items or with the other fatigue questionnaires studied.

## Acknowledgements

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### **Suppliers**

- <sup>a</sup> MSP 5.0 for Windows; ProGAMMA BV, A weg 43, PO Box 841, 9700AV Groningen, The Netherlands.
- <sup>b</sup> SPSS Inc, 233 S Wacker Dr, 11th Fl, Chicago, IL 60606.



## CHAPTER 4

### Reproducibility of maximal quadriceps strength and its relationship to maximal voluntary activation in postpoliomyelitis syndrome

Herwin Horemans, Anita Beelen, Frans Nollet,  
David Jones, and Gustaaf Lankhorst

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## ABSTRACT

**Objectives:** To determine what changes in maximal isometric strength can be detected in a symptomatic quadriceps muscle in patients with postpoliomyelitis syndrome (PPS) and to investigate the association between the variability in maximal strength and maximal voluntary activation (MVA).

**Design:** Repeated-measures over a 3-week interval.

**Setting:** University hospital.

**Patients:** Convenience sample of 65 patients with PPS.

**Intervention:** Dynamometer testing.

**Main outcome measures:** Maximal voluntary contraction (MVC) torque of the quadriceps was measured with a Kin-Com dynamometer and MVA was determined by twitch interpolation.

**Results:** The mean difference between the 2 consecutive measurements was  $-0.7 \pm 12.8$  Nm (95% confidence interval [CI], -3.9 to 2.5). The test-retest reliability was excellent for MVC torque (intraclass correlation coefficient [ICC]=.96; 95% CI, .93-.98) and moderate for MVA (ICC=.73; 95% CI, .56-.85). The smallest detectable change in MVC torque was 25% for an individual. The variability in MVA explained 18% of the variability in maximal strength.

**Conclusions:** Variability in maximal quadriceps strength, measured with a fixed dynamometer, was large and partly related to variability in MVA. This implies that even with optimally standardized strength testing, a follow-up of many years is required to objectify progression of quadriceps weakness in an individual patient with PPS. To demonstrate changes in strength in groups of patients in follow-up or intervention studies, feasible sample sizes are required.

People who suffered from acute poliomyelitis earlier in their lives may develop new neuromuscular symptoms after decades of neurologic and functional stability. This late deterioration is referred to as postpoliomyelitis syndrome (PPS), and it is characterized by new or increased muscle weakness that is due to a slow, progressive loss of muscle fibres.<sup>1-4</sup>

The diagnostic criteria for PPS have recently been revised, and now include the criterion that new symptoms should persist for at least 1 year.<sup>5</sup> However, it is questionable whether an individual decline in strength can be identified over such a short period. Long-term studies have estimated that the decline in strength is only 1% to 2% per year.<sup>6,7</sup> Therefore, highly sensitive measurements are required to demonstrate progression. Manual muscle testing and hand-held dynamometry have limitations with respect to their test-retest reliability and ability to detect change in muscle strength.<sup>8-11</sup> In contrast, fixed dynamometers have shown good test-retest reliability when used to measure strength in several patient groups, based on intraclass correlation coefficients (ICCs) and the coefficients of variation.<sup>12,13</sup> However, data on reproducibility of measurements with a fixed dynamometer in PPS are scarce,<sup>14</sup> and there are no data on the ability to detect change of strength within an individual. Knowledge of reproducibility is essential, not only to determine the ability of the instrument to detect individual changes, but also to determine sample sizes for intervention studies.

Measurements of maximal voluntary strength make the assumption that the subject is able to fully activate the muscle. However, in subjects with multiple sclerosis and subjects with a history of polio, especially those with PPS, studies have shown impaired voluntary muscle activation.<sup>15-17</sup> In healthy subjects, the test-retest reliability of maximal voluntary activation (MVA) of the quadriceps, using a bipolar twitch interpolation technique,<sup>18</sup> was found to be good (ICC=.96).<sup>19</sup> However, the reproducibility of measurements in patients with PPS has not yet been addressed.

Variability in voluntary activation must lead to variability in voluntary strength, and may therefore contribute to the variability in muscle performance of symptomatic muscles in patients with PPS, but this relationship has not yet been investigated.



Therefore, the main objective of our study was to investigate the reproducibility of measurements of maximal voluntary strength and MVA of the quadriceps muscle with symptoms of postpoliomyelitis muscle dysfunction in patients with PPS, using a fixed dynamometer. The second objective was to investigate the association between variability in strength and voluntary activation.

## METHODS

### Participants

Sixty-five patients with PPS (42 women, 23 men), according to the criteria defined by Halstead<sup>4,20</sup> and colleague, participated in the study. Additional inclusion criteria for all patients were: (1) symptoms of postpoliomyelitis muscle dysfunction<sup>21</sup> (ie, new muscle weakness, new muscle fatigue, new muscle pain, or new atrophy) in at least 1 quadriceps muscle with a minimum strength of 30Nm; (2) age between 18 and 70 years; and (3) no symptoms of joint pain in the hip or knee or significant neurologic or orthopedic disorders. Subjects' mean age  $\pm$  standard deviation (SD) was  $52 \pm 8$  years (range, 36-68 years), the mean time since the onset of polio was  $49 \pm 8$  years (range, 22-66 years), and the mean time since the onset of new neuromuscular symptoms was  $10 \pm 6$  years (range, 1-30 years). If both quadriceps muscles were symptomatic, the quadriceps with the severest symptoms was investigated. The medical ethics committee of the hospital approved the study, and all patients gave their written informed consent.

### Quadriceps strength

Strength of the quadriceps was measured with a Kin-Com dynamometer<sup>a</sup> with the subjects seated in an upright position. The axis of the dynamometer was aligned with the lateral femoral condyle. Subjects held on to 2 handgrips, 1 on each side of the seat, and were belted into the chair with an adjustable strap around the waist for stabilization. The force transducer was positioned just proximal and ventral to the malleoli. For each subject, the height of the axis of the dynamometer, the distance between the midpoint of the force transducer and the axis, and the adjustments of the

chair were recorded. Force data were sampled at 1kHz and stored on a personal computer.

Each subject performed 3 maximal isokinetic contractions ( $30^{\circ}/s$ ) of the quadriceps between  $100^{\circ}$  and  $30^{\circ}$  of knee flexion to determine the optimal angle to generate maximal force. The optimal knee angle was individually defined as the angle at which peak torque occurred (mean of 3 attempts), and was used in all measurements. After a 5-minute rest interval, subjects performed 6 isometric maximal voluntary contractions (MVCs) of the quadriceps (MVC torque), with a 2-minute rest between tests. MVC torque was determined as the highest peak torque of the 6 trials (figure 1A).

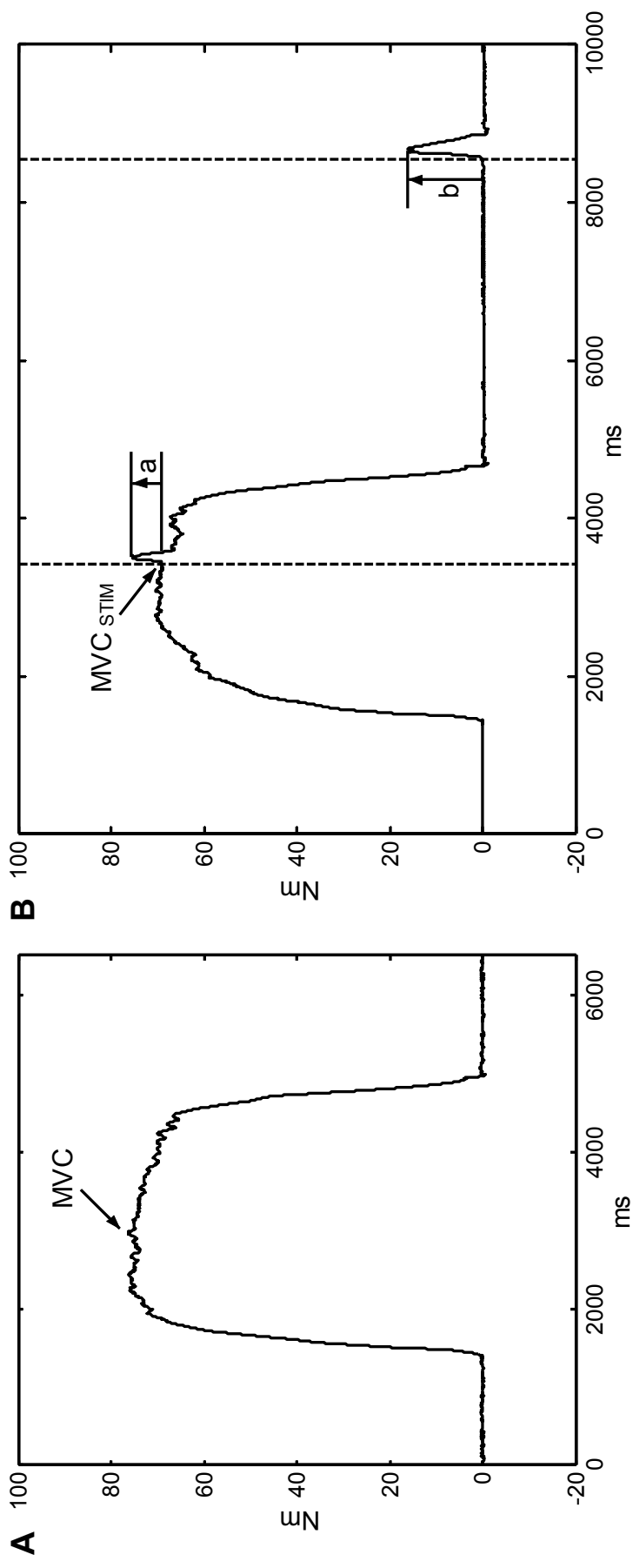
### **Maximal voluntary activation**

MVA of the quadriceps was measured during the last 3 maximal contractions, using a twitch interpolation technique modified from the method described by Allen et al.<sup>16</sup>

The quadriceps muscles were stimulated percutaneously with a Digitimer constant current stimulator,<sup>b</sup> using 2 stimulating electrodes (one  $12 \times 12$ cm and one  $10 \times 10$ cm aluminum foil electrode applied on dampened absorbent sponge tissue) placed over the anterior thigh. Unidirectional square-wave pulses of  $50\mu s$  were used at a voltage of 200V. The current was chosen such that, with a 1-second 30-Hz stimulation, at least 25% of the MVC torque was achieved.

During an MVC, 100-Hz stimulation was applied at the time of peak torque for 40ms. Five seconds after the first stimulation, an identical stimulation was delivered to the relaxed quadriceps to evoke a control tetanus. Voluntary activation was calculated from the increment in torque produced by stimulation at the moment of peak torque and the torque due to the control stimulation (figure 1B). MVA was determined as the highest voluntary activation of the 3 trials.

Maximal voluntary strength and MVA of the quadriceps were measured twice 3 weeks apart. The same individually determined settings of the dynamometer were used for both visits.



**Figure 1** Measurements of MVC torque and MVA. (A) The MVC torque is determined as the highest peak torque of 3 trials. (B) MVA is calculated from the increment in torque produced by stimulation during an MVC (a) and the torque due to control stimulation (b) as  $(1-a/b) \times 100$ .  $MVC_{STIM}$  is the voluntary torque at the start of stimulation.

## Data analysis

Systematic differences between visits were analyzed by paired  $t$  tests. For each visit, the MVC torque was compared (paired  $t$  test) with the voluntary torque at the start of stimulation (MVC<sub>STIM</sub> torque) in the MVA trial. The test-retest reliability was assessed by calculating the ICC and the 95% confidence interval (CI) of the ICC, using a random effects 1-way analysis of variance.<sup>22</sup> A lower limit of the CI of at least .75 is considered to be good test-retest reliability.<sup>23,24</sup>

To assess the smallest change that can be detected within an individual, the 95% limits of agreement for repeated MVC torque and MVA were analyzed according to the Bland and Altman method.<sup>25</sup> For each subject, the difference between the 2 visits was plotted against the mean of the 2 visits. For normally distributed differences, 95% of the differences will lie between:  $\text{mean}_{(\text{visit 2}-\text{visit 1})} \pm 2 \text{ SD}$ . Because the magnitude of the difference in MVC torque increased with increasing mean values, the 95% limits of agreement were calculated after log transformation of the data as:  $\text{mean}_{(\log[\text{visit 2}]-\log[\text{visit 1}])} \pm 2 \text{ SD}$ , and expressed as ratios after taking the antilog of the resulting values.<sup>25</sup>

Estimates of sample size were made for an effect study comparing 2 independent groups. The minimal total number of subjects needed ( $n$ ) to find a significant difference in change of MVC torque between groups was calculated from the formula:  $n > 4(Z_{\alpha} + Z_{\beta})^2 \text{SD}^2 / \delta^2$ , with  $Z$  values based on tables of standard normal curves ( $Z_{\alpha} + Z_{\beta} = 3.242$  for  $\alpha = .05$  and  $\beta = .10$ ),  $\text{SD}$  as the  $\text{SD}$  of the difference, and  $\delta$  as the minimal difference in effect between groups that is considered of clinical interest.<sup>26,27</sup>

The relationship between the difference in MVA between visits and the difference in MVC<sub>STIM</sub> torque between visits was studied by calculating the Pearson correlation coefficient. Statistical significance was defined at the  $P$  less than .05 level. For statistical analysis the SPSS, version 10.0.5, software package<sup>c</sup> was used.

## RESULTS

The mean knee angle  $\pm \text{SD}$  of the quadriceps to generate maximal force was  $54^{\circ} \pm 11^{\circ}$  of flexion (range,  $30^{\circ}$ - $74^{\circ}$ ).

## Quadriceps strength

The mean difference in MVC torque between the 2 measurements (second minus first measurement) was  $-0.7 \pm 12.8$  Nm (95% CI, -3.9 to 2.5) (table 1). The test-retest reliability of MVC torque was excellent, according to the ICC.

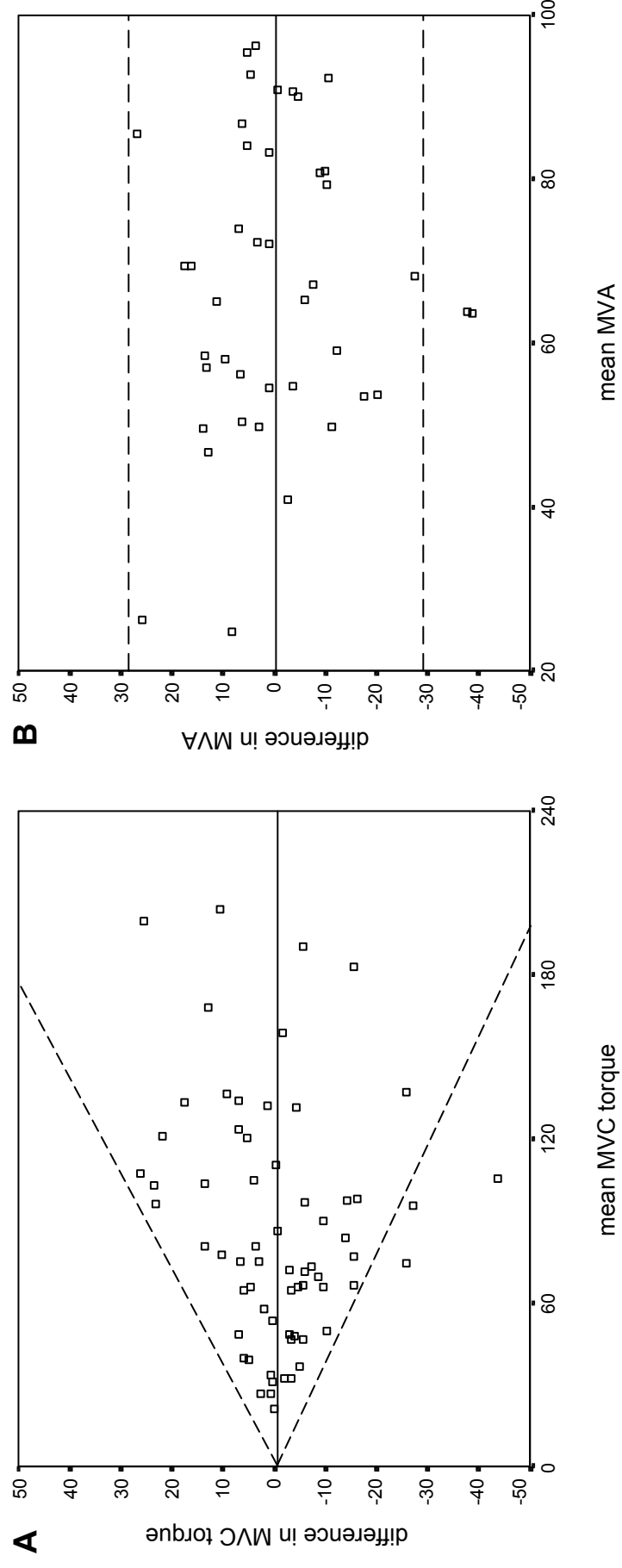
**Table 1** Score per visit and test-retest reliability

|  | Visit 1<br>(range)              | Visit 2<br>(range)              | $\Delta$ Visit 2-Visit 1 | 95% CI $_{\Delta}$ | ICC | 95%<br>CI $_{ICC}$ |
|--|---------------------------------|---------------------------------|--------------------------|--------------------|-----|--------------------|
| MVC torque<br>(n=65)                               | 87.3 $\pm$ 43.5<br>(21-199)     | 86.6 $\pm$ 45.6<br>(21-213)     | -0.7 $\pm$ 12.8          | -3.9 to 2.5        | .96 | .93-.98            |
| MVA<br>(n=42)                                      | 67.3 $\pm$ 20.1<br>(13.3-97.6)  | 67.1 $\pm$ 18.9<br>(28.8-98.9)  | -0.3 $\pm$ 14.4          | -4.7 to 4.2        | .73 | .56-.85            |
| MVC <sub>STIM</sub> torque<br>(n=42)               | 76.4 $\pm$ 37.8<br>(23.0-170.6) | 73.0 $\pm$ 35.9<br>(24.0-175.1) | -3.4 $\pm$ 15.7          | -8.3 to 1.5        | .91 | .84-.95            |
| Torque due to the<br>control stimulation<br>(n=42) | 16.6 $\pm$ 7.4<br>(5.0-38.5)    | 17.6 $\pm$ 7.2<br>(5.4-36.0)    | 1.0 $\pm$ 4.7            | -0.4 to 2.5        | .79 | .64-.88            |

The score on the 2 visits and the difference ( $\Delta$ ) are presented as mean  $\pm$  SD in newton meters, and the 95% CI of  $\Delta$  (CI $_{\Delta}$ ) is given. The ICC and the 95% CI of the ICC (CI $_{ICC}$ ) are given.

The distribution of the difference in MVC torque between the 2 measurements is shown in figure 2A. The 95% limits of agreement, expressed as ratios after log transformation of the data, were 0.75 and 1.29. According to these limits, the smallest decline in MVC torque that can be detected within an individual is 25%.

From the 95% CI around the mean, it follows that the smallest decline in quadriceps strength that can be detected at group level is 3.9 Nm (4.5%) (table 1). According to the minimal change ( $\delta$ ) that is considered of clinical interest, the total number of subjects needed in an intervention study would be greater than  $4 \times 3.242^2 \times 12.8^2 / \delta^2$ . For example, to demonstrate a 10% difference in the change in quadriceps strength between 2 groups as statistically significant, a total of 92 subjects (2 groups of 46 subjects) would be needed.



**Figure 2** Bland-Altman plots of repeated measures of (A) MVC torque and (B) MVA. Original data are presented. The solid line represents the mean difference (the second visit minus the first visit), the dotted lines represent the 95% limits of agreement. The limits of agreement for MVC torque are expressed as ratios.

### Maximal voluntary activation

MVA was determined in 42 patients. MVA could not be determined in 22 patients because the required 25% of maximal torque could not be reached with stimulation. For these subjects, either the torque-current relationship reached an early maximum, for example, there was no further increase in torque at higher currents ( $n=19$ ), or a higher current was not tolerated ( $n=3$ ). Data were missing for 1 subject, due to a recording failure. The MVC torque of the 23 patients whose MVA could not be determined was comparable to the MVC torque of the other 42 patients.

The 30 Hz stimulation of the relaxed quadriceps during 1 second yielded  $34\% \pm 7\%$  of MVC torque on the first study visit and  $36\% \pm 8\%$  of MVC torque on the second study visit. MVC<sub>STIM</sub> torque was significantly lower than MVC torque on both study visits ( $P < .01$ ). MVC<sub>STIM</sub> torque was  $90.9\% \pm 14.8\%$  of MVC torque on the first visit and  $90.1\% \pm 11.6\%$  of MVC torque on the second visit.

The test-retest reliability of MVA and the torque due to the control stimulation were moderate, according to the ICC (table 1). The distribution of the difference in MVA between visits is shown in figure 2B. The limits of agreement between the 2 MVA measurements were -29.0 and 28.5.

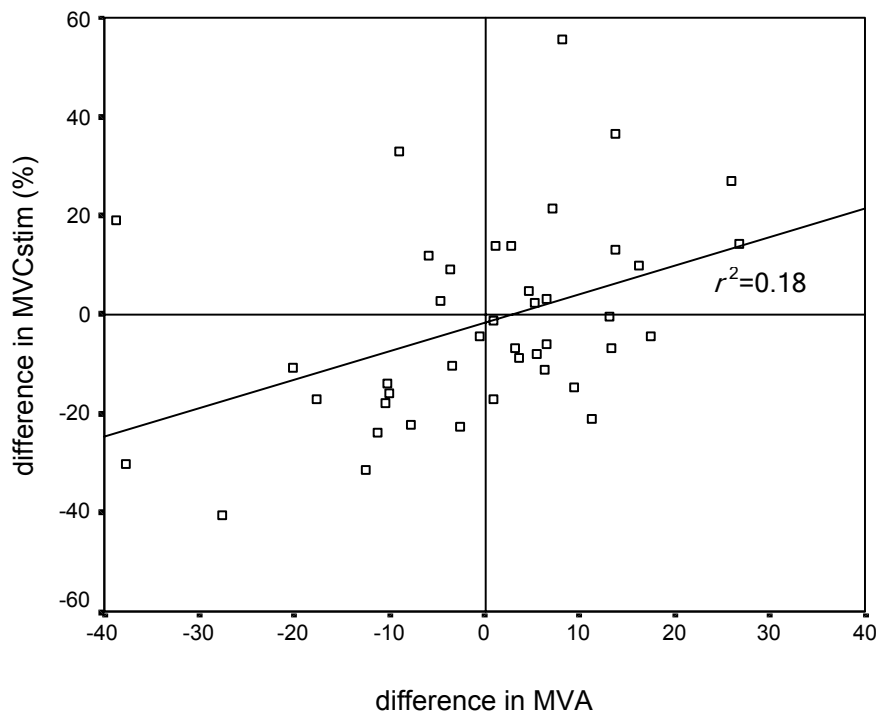
The correlation coefficient of the difference in MVA between the 2 measurements and the difference in MVC<sub>STIM</sub> torque between the 2 measurements was .42 ( $P < .01$ ) (figure 3). Therefore, 18% ( $r^2$ ) of the variance in MVC<sub>STIM</sub> torque was explained by the variance in MVA.

## DISCUSSION

Many patients with PPS complain of progressive muscle weakness. However, the rate of strength loss appears to be slow, and therefore highly sensitive measurements are required to demonstrate a decline.

The first objective of this study was to determine the reproducibility of MVC torque of symptomatic quadriceps muscles in patients with PPS, using a fixed dynamometer. The ICC for MVC torque measurements found in this study indicated excellent test-retest reliability at group level, which is in accordance with the findings of other studies with regard to the reliability of fixed dynamometry.<sup>14,28</sup> However, the large

between-subjects variance in MVC torque, due to extensive differences in the degree of paresis, assures a high correlation, because the ICC is determined as the ratio of the between-subjects variance to the between-subject variance plus error variance.<sup>22</sup>



**Figure 3** The difference in MVA between visits is plotted against the difference in MVC<sub>STIM</sub> torque. The difference in MVA is calculated from the score on the second visit minus the score on the first visit. The difference in MVC<sub>STIM</sub> torque is expressed as the percentage of change from the first visit. The squared correlation coefficient ( $r^2$ ) indicates the variance in MVC<sub>STIM</sub> torque that is explained by the variance in MVA.

To focus in particular on the error variance, the differences in MVC torque between visits were plotted against their mean.<sup>25</sup> The limits of agreement calculated from this plot (0.75-1.29) were wide when compared with the smallest detectable difference found for isometric quadriceps strength in healthy subjects (14%).<sup>29</sup> The limits of agreement were only slightly better than for hand-held dynamometry in polio survivors (limits of agreement, 0.76-1.52).<sup>11</sup> This was surprising, because the



variability due to measurement error is expected to be less for fixed than for hand-held dynamometry because of better standardization. Apparently, the within-subject variability is a major determinant of the reproducibility of maximal strength measurements in polio subjects.

The finding that a change of at least 25% is required to detect an individual change in MVC torque illustrates the lack of reproducibility at the individual level. To demonstrate a deterioration in quadriceps strength at the group level in the study sample, a mean decline of 4.5% would be required. Because the rate of strength loss is estimated at 1% to 2% per year,<sup>6,7</sup> a follow-up of several years would be needed to demonstrate a decline. In fact, studies<sup>6,7,30</sup> that have reported a significant decline in maximal strength all had follow-up durations of at least 4 years. The negative outcomes in studies with a follow-up of less than 4 years and/or small sample sizes may have been due to a lack of power.<sup>31-33</sup>

Another consequence of reproducibility is that it determines the minimum number of subjects required for randomised controlled trials. Despite the poor reproducibility at the individual level, feasible sample sizes are needed to demonstrate a relevant improvement in studies comparing 2 independent groups.

One factor that may account for the variability of repeated MVC torque is variability in voluntary activation. Unfortunately, activation levels could only be determined in 42 patients, mainly because it was often impossible to stimulate sufficient muscle mass. This might be caused by the presence of subcutaneous and intramuscular fat tissue originating from denervated muscle fibres.<sup>34,35</sup>

The MVA scores in our study were low, compared with those reported for the elbow flexor muscles in patients with PPS.<sup>16,33</sup> In addition to intermuscle differences in MVA between the quadriceps and biceps,<sup>36</sup> it seems likely that the lower strength values obtained in the trials in which stimulation was applied, compared with the values obtained in the trials without stimulation, have played a role. This has also been observed by Yue et al.<sup>37</sup> Awareness of the forthcoming electric stimulation may have prevented subjects from producing maximal exertions. However, it may also be that the ability to exert maximal voluntary strength declined during the measurements,

due to increasing fatigue, especially because all muscles investigated showed symptoms of postpoliomyelitis muscle dysfunction.

The reliability of MVA was moderate: the ICC (.73) was lower than that reported for quadriceps muscles of healthy subjects (ICC range, .86-.96).<sup>19,38</sup> Only 18% of the variability in MVC<sub>STIM</sub> torque was explained by the variability in MVA. This is not consistent with the assumption of the twitch interpolation technique that voluntary activation and voluntary force are strongly correlated. The limited contribution of MVA to the variability in maximal voluntary strength may be due to the curvilinear relationship between relative force (force as a percentage of the maximal “true” force) and voluntary activation.<sup>19,39-41</sup> This implies that the variability in voluntary activation is not linearly related to the variability in voluntary force in a healthy muscle. However, it is unknown whether the curvilinear relationship between relative force and voluntary activation is similar for healthy and symptomatic muscles. Furthermore, in our study the knee angle was individually adjusted to optimal muscle length, and therefore differed between subjects. There are indications that the force-activation relationship is influenced by muscle length.<sup>39,42</sup>

Another reason for the relatively small contribution of the MVA variability to the variability in maximal voluntary strength may be the possibility of coactivation of the hamstring muscles, which was not measured. Antagonistic coactivation decreases the voluntary extension torque output on the dynamometer, but has no effect on the MVA. It has been reported that, during maximal isometric knee extension, subjects demonstrate significant antagonistic coactivation (20%–40% depending on age).<sup>43,44</sup>

## CONCLUSIONS

Even in optimal standardized conditions, strength measurements made with a fixed dynamometer are unable to detect small changes in the strength of symptomatic quadriceps muscles in individual patients with PPS. However, the reproducibility is sufficient to evaluate changes in groups of subjects in both follow-up and intervention studies.

The variability in maximal strength was related to the variability in MVA, although only to a limited extent. Several factors may have influenced the findings, and further

research should be carried out, for instance, to determine the relationship between voluntary activation and contraction torque as a function of muscle length and to assess the level and variability of antagonistic coactivation. This may improve our understanding of the variability in maximal strength of patients with PPS.

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## Suppliers

- <sup>a</sup> Kinetic Communicator; Chattecx Corp, Chattanooga Group, 4717 Adams Rd, Hixson, TN 37343.
- <sup>b</sup> DS7A; Digitimer Ltd, Welwyn Garden City, Hertfordshire, England.
- <sup>c</sup> SPSS Inc, 233 S Wacker Dr, 11th Fl, Chicago, IL 60606.



## CHAPTER 5

### Reproducibility of walking at self-preferred and maximal speed in patients with postpoliomyelitis syndrome

Herwin Horemans, Anita Beelen, Frans Nollet,  
and Gustaaf Lankhorst

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## ABSTRACT

**Objective:** To assess the reproducibility of walking performance, heart rate, and perceived exertion at self-preferred speed and maximal walking speed in patients with the postpoliomyelitis syndrome (PPS).

**Design:** Repeated measurement at a 3-week interval.

**Setting:** University hospital.

**Participants:** Convenience sample of 65 patients with PPS.

**Interventions:** Not applicable.

**Main outcome measures:** Walking performance: the distance walked in 2 minutes at a self-preferred speed and the time needed to walk 75m at maximal speed, heart rate, and rating of perceived exertion (RPE) on an 11-point scale.

**Results:** Test-retest reliability of walking performance was excellent for both tests (intraclass correlation coefficient [ICC] range, .94-.97). No systematic differences existed between test and retest. The smallest detectable change for an individual was 15% for both tests. Test-retest reliability for heart rate was good (ICC=.86) but moderate for RPE (Spearman  $\rho$  range, .67-.70). The smallest detectable change for RPE was between 4 and 6 scale points. The variability in walking performance was significantly correlated with the variability in heart rate at self-preferred speed ( $r=.36$ ,  $P<.01$ ) but not with the variability in RPE ( $r=.20$ ,  $P=.11$ ).

**Conclusions:** Both walking tests showed good reproducibility and may be appropriate to monitor (individual) changes in walking capacity in patients with PPS. Because of its moderate reproducibility, RPE does not seem to be suitable to monitor physical exertion. The usefulness of an objective measure such as heart rate for this purpose needs further investigation.

Increased difficulty with walking is among the major functional problems persons with the postpoliomyelitis syndrome (PPS) experience.<sup>1-4</sup> In particular, the decrease in ability to walk outdoors is perceived as a major problem by patients with PPS<sup>5</sup> and may affect their level of independence and life satisfaction.<sup>6</sup>

In cross-sectional studies of patients with PPS, walking performance has been measured in a laboratory setting for both self-preferred speed and maximal speed.<sup>5,7,8</sup> Whether such tests are appropriate in longitudinal studies, for instance to determine a decline in walking capacity, depends largely on their reproducibility. Although the reproducibility of walking tests at self-preferred and maximal speed is good in patients with respiratory disease,<sup>9</sup> chronic heart failure,<sup>10</sup> and neurologic impairment,<sup>11</sup> no data on the reproducibility of the tests are available in patients with PPS.

In addition to walking performance, it may also be relevant to assess physical effort, which relates to the length of time that the activity can be sustained. Physical effort can be measured objectively by recording the heart rate, but also at the level of perception, by rating the perceived exertion (RPE). The RPE has been used to determine exercise levels in PPS patients.<sup>12</sup> Recently, the March of Dimes Birth Defects Foundation recommended use of an RPE scale<sup>13</sup> for daily life activities to avoid excessive fatigue in patients with PPS.<sup>14</sup> Whether an RPE scale is appropriate for this purpose depends on its stability across measurements and on its relation with the actual effort and performance. Unfortunately, no information exists regarding the reproducibility of the RPE in PPS patients. Further, the literature has revealed inconsistencies about the strength of the relation between the RPE and physiologic criterion measures, such as heart rate.<sup>15,16</sup> Knowledge of the reproducibility of RPE and its relation to walking performance and heart rate during walking, may provide supportive evidence for its use to avoid overloading in patients with PPS.

The objective of the present study was to determine the test-retest reproducibility of 2 walking tests with respect to performance and physical effort in patients with PPS. One test measured the distance covered in 2 minutes when walking at a self-preferred speed, and the other test measured the time needed to walk 75m as fast as possible. We also investigated associations between the variability in performance

and the variability in physical effort, measured by means of heart rate (only at self-preferred speed) and RPE.

## METHODS

### Participants

Sixty-five subjects with PPS, according to the criteria defined by Halstead,<sup>17,18</sup> participated in the study. Inclusion criteria were (1) symptoms of postpoliomyelitis muscle dysfunction<sup>19</sup> (ie, new muscle weakness, new muscle fatigue, new muscle pain, or new atrophy) in at least 1 quadriceps, (2) ability to walk for at least 2 minutes, (3) age between 18 and 70 years, and (4) no significant other neurologic disorders. Use of walking aids and orthotic and orthopedic devices was allowed. The Medical Ethics Committee of the hospital approved the study, and all subjects gave written informed consent.

### Protocol

Two walking tests were performed on 2 visits that were separated by a 3-week interval. The tests were performed on a closed, marked, 65-m indoor trajectory and were started after the subjects had been sitting on a chair to rest for 5 minutes.

First, subjects walked at a self-preferred walking speed for 2 minutes, and the walking distance was measured. Then, after a 5-minute rest interval, they walked at their maximal walking speed (without running) over a distance of 75m, and the time needed to walk that distance was measured with a stopwatch. They were allowed to use walking aids and devices during the tests as they would when walking outdoors. Heart rate was recorded in both tests. After each walking test, the subjects rated their perceived exertion (RPE) on an 11-point scale deduced from Borg,<sup>13</sup> ranging from 0 (no exertion) to 10 (maximal exertion). The measurements on the second visit were scheduled at the same time of day as those on the first visit, and subjects walked with the same walking aids and devices on both visits.

## Data analysis

The heart rate during walking at self-preferred speed showed a steady state after 60 seconds. Therefore, the mean heart rate between 70 and 100 seconds was calculated and used in the analysis. No heart rate was analyzed for the test at maximal speed because no steady state could be observed.

The test-retest reliability for walking distance, walking time, and heart rate was assessed by the intraclass correlation coefficient (ICC) and the 95% confidence interval (CI) of the ICC, by using a random effects 1-way analysis of variance.<sup>20</sup> A lower limit of the CI of at least .75 is considered as good test-retest reliability.<sup>21,22</sup> The test-retest reliability of RPE was analyzed by calculating the Spearman correlation coefficient.

Systematic differences between visits were tested with the Student *t* tests for walking distance, walking time, and heart rate, and with the Wilcoxon signed-rank test for RPE. For walking performance and heart rate, agreement of measurements was analyzed according to the Bland-Altman method.<sup>23</sup> The 95% limits of agreement (LOA) were calculated as mean (visit 2-visit 1)±2 standard deviations (SDs) to determine the smallest change that can be detected within an individual. For the RPE, agreement of measurements was analyzed by calculating the 2.5 and 97.5 percentiles of the difference between the 2 visits.

Associations between walking performance, RPE, and heart rate were determined with respect to differences between visits by calculating the Pearson correlation coefficients. Statistical significance was defined at the *P* less than .05 level. For statistical analysis SPSS, version 10.0.5,<sup>a</sup> was used.

## RESULTS

Sixty-three subjects (40 women, 23 men) completed the walking tests on both study visits. Heart rate data on 3 subjects were missing because of recording failures.

The mean age of the subjects was 52±7 years. The mean time since the onset of polio was 49±8 years, and the mean time since the onset of symptoms of postpoliomyelitis muscle dysfunction was 10±6 years. Thirty-three patients (52%) wore orthopedic footwear, 14 patients (22%) walked with an ankle-foot or knee-ankle-

foot orthosis, and 9 patients (14%) used a cane or crutches. Nineteen patients (30%) did not use any orthopedic devices or walking aids.

### Walking at self-preferred speed

According to the ICCs, test-retest reliability was excellent for walking distance and good for heart rate (table 1). Test-retest reliability for RPE was satisfactory ( $r=.67$ ,  $P<.01$ ). The mean level of perceived exertion corresponded to “light exertion” (score, 3). There were no systematic differences between visits in walking distance, heart rate, or RPE.

**Table 1.** Results for walking at self-preferred speed

| Outcomes             | Visit 1                    | Visit 2                    | $d^*$                          | 95% CI <sub>d</sub><br>and $P$ | 95% LOA              | ICC      | 95% CI <sub>ICC</sub> |
|----------------------|----------------------------|----------------------------|--------------------------------|--------------------------------|----------------------|----------|-----------------------|
| Walking distance (m) | 119.2±23.9<br>(52.5-158.8) | 120.2±23.9<br>(60.0-166.1) | 1.0±8.5                        | -1.2, 3.1;<br>.38              | -16.1, 18.0          | .94      | .90–.96               |
| Heart rate (n=60)    | 102±16<br>(77-144)         | 100±13<br>(74-137)         | -2±8                           | -4, 0;<br>.06                  | -18, 14              | .86      | .77–.91               |
| Outcomes             | Visit 1 <sup>†</sup>       | Visit 2 <sup>†</sup>       | $d_{\text{median}}^{\ddagger}$ | $P^{\parallel}$                | 95% LOA <sup>¶</sup> | $r^{**}$ |                       |
| Perceived exertion   | 2 (1, 5)<br>(0-9)          | 2 (1, 5)<br>(0-10)         | 0 (-1, 1)                      | .45                            | -5, 4                | .67      |                       |

Values are mean ± SD (range) unless otherwise noted.

\* Mean difference ( $d$ ) between visits (second visit minus first visit).

† Median, 25th and 75th percentile, and range.

‡ Median difference ( $d_{\text{median}}$ ) between visits with 25th and 75th percentile.

∥ Wilcoxon signed-rank test.

¶ 2.5th and 97.5th percentile of the difference.

\*\* Spearman correlation coefficient.

The mean of the 2 visits against the difference between the 2 visits for walking distance are plotted in figure 1A. The LOA represent the smallest change that can be detected within an individual.

For walking distance, the LOA were -16.1 (-13.5% of change from the mean) and 18.0m (15.1%); for heart rate, -18 and 14; and for RPE, -5 and 4 scale points (see table 1).

No significant correlation was found between the difference in walking distance at the 2 visits and the difference in RPE ( $r=.20$ ,  $P=.11$ ). A weak relation was found between the difference in walking distance and the difference in heart rate ( $r=.36$ ,  $P<.01$ ). The difference in heart rate did not correlate with the difference in RPE ( $r=.14$ ,  $P=.30$ ).

### Walking at maximal speed

The test-retest reliability for walking time and RPE was comparable to that for walking at self-preferred speed (table 2). The level of perceived effort corresponded to “more than average exertion” (score, 6). No systematic differences existed between the 2 visits.

**Table 2** Results for walking at maximal speed

| Outcomes           | Visit 1                   | Visit 2                   | $d^*$                          | 95% CI <sub>d</sub><br>and $P$ | 95% LOA              | ICC      | 95% CI <sub>ICC</sub> |
|--------------------|---------------------------|---------------------------|--------------------------------|--------------------------------|----------------------|----------|-----------------------|
| Walking time (s)   | 60.5±20.0<br>(38.2-167.4) | 60.7±18.2<br>(41.4-145.6) | 0.2±4.5                        | -1.0, 1.3;<br>.77              | -8.9, 9.2            | .97      | .96-.98               |
| Outcomes           | Visit 1 <sup>†</sup>      | Visit 2 <sup>†</sup>      | $d_{\text{median}}^{\ddagger}$ | $P^{\parallel}$                | 95% LOA <sup>¶</sup> | $r^{**}$ |                       |
| Perceived exertion | 7 (4, 8)<br>(0-10)        | 6 (4, 8)<br>(0-10)        | 0 (-1, 0)                      | .14                            | -6, 5                | .70      |                       |

See note to table 1.

Because there was no particular reason for the outlier that appeared on the scatter plot for walking time (see figure 1B), we included the data of this subject in the analysis. The LOA were -8.9 (-14.6% change from mean) and 9.2 seconds (15.2%)

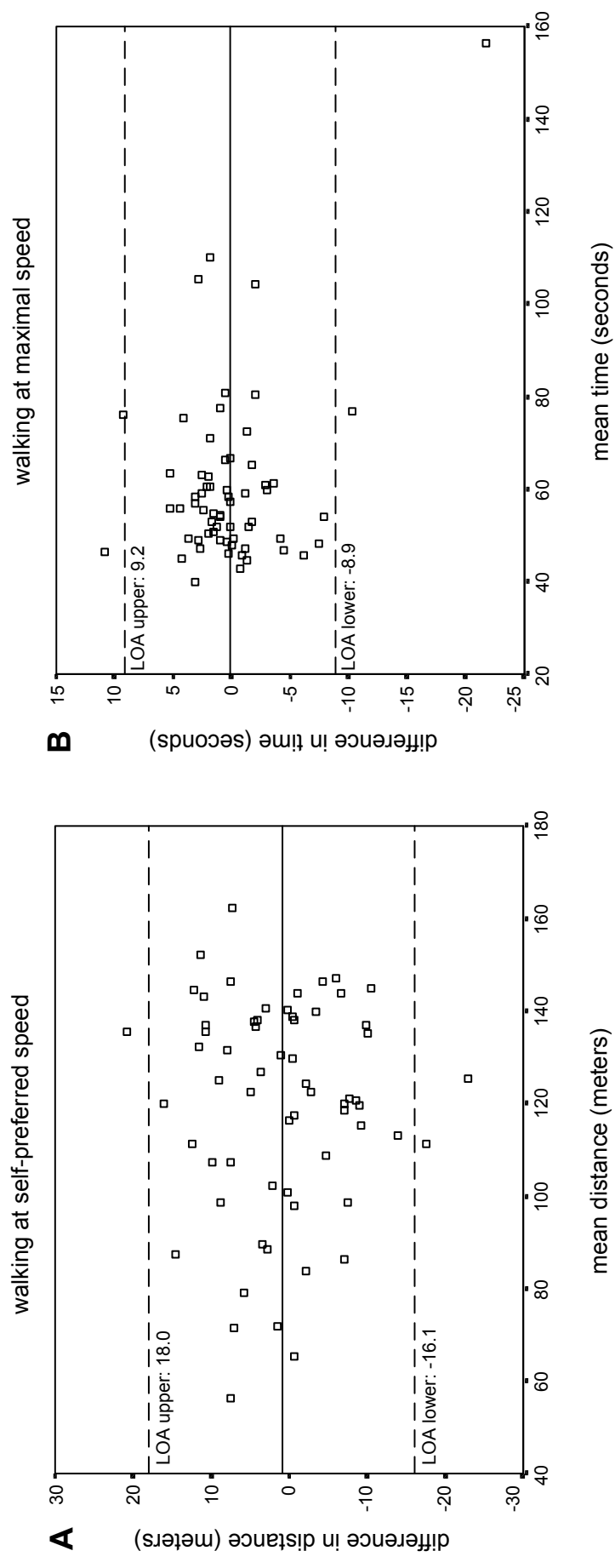
for walking time and -6 and 5 for RPE (see table 2). No correlation was found between the difference in walking time and the difference in RPE ( $r=.01$ ,  $P=.97$ ).

## DISCUSSION

The results showed that the test-retest reliability of walking performance and heart rate was good. The ICCs for walking performance in the present study were comparable to those reported for other populations.<sup>11,24,25</sup> In contrast to the findings of several other studies on reproducibility of walking performance,<sup>26-28</sup> no learning effects were found. Further, the smallest detectable change in walking performance at individual level was better than that obtained by strength measurements using a handheld dynamometer (smallest detectable changes of  $\geq 24\%$ ).<sup>29</sup> Compared with such strength measurements, the walking tests in the present study will detect deterioration in performance more readily and are, therefore, appropriate for comparing conditions at the individual and at the group levels.

It appeared that the smallest detectable change in walking performance was equal for self-preferred and maximal speed. We expected that walking at maximal speed would be less reproducible because it may be more susceptible to differences in motivation,<sup>10</sup> and patients may not be used to performing activities at maximal speed. On the other hand, variability in maximal walking speed may have been limited by the use of walking aids and orthotic devices and by certain limitations in joint mobility.

Although the reproducibility of walking performance and heart rate were good in the present study, the reproducibility of RPE was moderate. The wide LOA indicate that the individual effort that is perceived during a similar performance under the same circumstances varies considerably. Similar findings have been reported for healthy subjects.<sup>30,31</sup> Although one might expect the reproducibility of RPE to benefit from practice,<sup>32,33</sup> RPE does not seem to be a reliable measure of physical exertion in walking tests in patients with PPS. Although RPE correlates with local muscle fatigue,<sup>34</sup> its poor reproducibility in walking tests may result from variation in factors other than local muscle fatigue (eg, emotional state).<sup>35</sup>



**Figure 1** Bland-Altman plots for walking (A) at a self-preferred and (B) at maximal speed. The solid line represents the mean difference (second visit minus first visit); the dotted lines represent the 95% LOA.



To investigate whether the variability of walking performance was related to the variability in heart rate and the variability in RPE, correlations were calculated. As expected, an increase in walking performance was associated with an increase in heart rate. However, a change in walking performance did not correlate with a change in RPE. A reason for this finding may be that limited variation in walking speed is not likely to result in differences in perceived exertion.

A limitation of the analysis of the associations among performance, heart rate, and RPE is that only a part of a full relationship could be investigated. Preferably, these variables should be compared over larger scale ranges by measuring heart rate and RPE at predetermined intervals of walking speed.<sup>36</sup>

## CONCLUSIONS

Reproducibility of walking at different speeds was good in patients with PPS. Therefore, both walking tests are appropriate to monitor walking performance over time. Because no difference existed in reproducibility between the tests at different speeds, the choice of test must be based on other criteria. Testing at maximal speed might be more sensitive because one may assume that a strength decline in the muscles that are responsible for locomotion will affect walking performance at maximal speed more readily than at self-preferred speed. On the other hand, if the interest is primarily to study changes in actual walking performance, it might be preferable to use the walking test at self-preferred speed because it conforms more to the normal daily situation.

From the moderate reproducibility of RPE at the individual level, we conclude that this is not an appropriate tool to monitor the physical performance of patients with PPS to avoid overload of their physical capacity. Heart rate was a better indicator of physical effort. However, the appropriateness of heart rate as a way to monitor physical effort in patients with PPS must be determined in further studies.

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## Supplier

<sup>a</sup> SPSS Inc, 233 S Wacker Dr, 11th Fl, Chicago, IL 60606.



## CHAPTER 6

Pyridostigmine in postpoliomyelitis syndrome:  
no decline in fatigue and  
limited functional improvement

Herwin Horemans, Frans Nollet, Anita Beelen,  
Gea Drost, Dick Stegeman, Machiel Zwarts,  
Hans Bussmann, Marianne de Visser, and Gustaaf Lankhorst  
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## ABSTRACT

**Objectives:** To investigate the effect of pyridostigmine on fatigue, physical performance, and muscle function in subjects with postpoliomyelitis syndrome.

**Methods:** 67 subjects with increased fatigue and new weakness in one quadriceps muscle showing neuromuscular transmission defects, were included in a randomised, double blind, placebo controlled trial of 60 mg pyridostigmine four times a day for 14 weeks. Primary outcome was fatigue (on the “energy” category of the Nottingham Health Profile). Secondary outcomes included two-minute walking distance and quadriceps strength and jitter. Motor unit size of the quadriceps was studied as a potential effect modifier. The primary data analysis compared the changes from baseline in the outcomes in the last week of treatment between groups.

**Results:** 31 subjects treated with pyridostigmine and 31 subjects treated with placebo completed the trial. No significant effect of pyridostigmine was found on fatigue. The walking distance improved more in the pyridostigmine group than in the placebo group (by 7.2m (6.0%);  $P<0.01$ ). Sub-group analysis showed that a significant improvement in walking performance was only found in subjects with normal sized motor units. Quadriceps strength improved more in the pyridostigmine group than in the placebo group (by 6.7Nm (7.2%);  $P=0.15$ ). No effect of pyridostigmine was found on jitter.

**Conclusions:** Pyridostigmine in the prescribed dose did not reduce fatigue in subjects with postpoliomyelitis syndrome. However, it may have a limited beneficial effect on physical performance, especially in subjects with neuromuscular transmission defects in normal sized motor units.

Subjects with postpoliomyelitis syndrome<sup>1</sup> often complain of fatigue<sup>2-4</sup> and a deterioration in functional abilities.<sup>5-7</sup> These symptoms may, in part, reflect neuromuscular transmission defects.<sup>8-11</sup> The hypothesis in postpoliomyelitis syndrome is that the enlarged motor units which were formed during the recovery phase lose their ability to maintain all their sprouts, which slowly deteriorate.<sup>12</sup> This deterioration may be accompanied by increasing neuromuscular transmission defects as a result of progressive dysfunction of acetylcholine synthesis and release.<sup>12-14</sup> The severity of these transmission defects might increase with increasing motor unit size.<sup>15</sup> Furthermore, polio patients, especially those with postpoliomyelitis syndrome, are often unable to activate their muscles fully, which may be related to neuromuscular transmission defects.<sup>16</sup>

Pyridostigmine, an anticholinesterase inhibitor, prolongs the effectiveness of acetylcholine. In open studies of pyridostigmine in patients with postpoliomyelitis syndrome, both neuromuscular transmission defects and perceived fatigue decreased.<sup>8,17,18</sup> However, a randomised double blind trial failed to confirm a beneficial effect.<sup>19</sup> In that study, patients were not selected on the basis of a predefined level of fatigue or on the presence of neuromuscular transmission defects, and the responsiveness of the primary outcome measure, the short form 36 item questionnaire (SF-36), may have been insufficient to detect change.<sup>20-22</sup> Furthermore, the investigators questioned the adequacy of 180 mg of pyridostigmine a day.<sup>19</sup>

The present placebo controlled double blind trial was undertaken to study the effect of 240 mg pyridostigmine a day in a selected group of subjects with postpoliomyelitis syndrome who had an increased level of fatigue and proven neuromuscular transmission defects in a symptomatic quadriceps muscle—a muscle that is functionally important for locomotion. Our primary aim was to investigate the effect of pyridostigmine on perceived fatigue. Secondary objectives were to investigate the effects on physical performance and muscle function.



## METHODS

### Patient selection and baseline assessment

Ambulatory subjects with postpoliomyelitis syndrome were included if they had the following:

- a fatigue score of 10 points or more on the short fatigue questionnaire<sup>23</sup>
- symptoms of postpoliomyelitis muscle dysfunction<sup>24</sup> in at least one quadriceps muscle
- neuromuscular transmission defects (mean jitter  $>30\mu\text{s}$  or more than two jitter values of  $>40\mu\text{s}$ ) in the symptomatic quadriceps muscle on single fibre electromyographic stimulation (S-SFEMG)<sup>25,26</sup>
- a minimum quadriceps strength of 30Nm
- age between 18 and 70 years

Exclusion criteria were significant neurological, orthopaedic, cardiovascular, pulmonary, or endocrine disorders, and anaemia or thyroid dysfunction, both checked by blood tests. The quadriceps with the severest symptoms was investigated.

The duration of symptoms of postpoliomyelitis syndrome, the severity of paresis of the legs, and motor unit size of the lateral vastus were recorded at baseline. The severity of paresis was calculated as a sum score of 16 lower extremity muscle groups,<sup>4</sup> based on manual muscle testing.<sup>27</sup> The size of at least 10 motor units was estimated from multichannel surface EMG recordings.<sup>28</sup> Enlarged mean motor unit size was defined as  $>4\text{ mV}\cdot\text{ms}$ .<sup>28</sup>

The medical ethics committees of the hospitals involved approved the study. All subjects gave their written informed consent.

### Randomisation, blinding, and treatment regimen

Randomisation of treatment allocation was done in blocks of four. All treatment allocations were concealed for the patients as well as the researchers. The data analyst remained blinded until after the primary outcome analyses.

A dose of 60 mg pyridostigmine four times a day was given for 14 weeks. The dose was gradually increased during the first six days from 4x10 mg to 4x60 mg, to

reduce the chance of adverse effects. From the fourth day onwards, 0.125 mg atropine was added at each dose to mask the parasympathetic effects of pyridostigmine. The placebo-treated subjects also received pyridostigmine during the first three days in the same incremental dose to improve blinding. Subsequently, the pyridostigmine was phased out in two days, and from day 6 onwards placebo pyridostigmine was given. From day 4 onwards this was combined with placebo atropine. Drug treatment was taken 1.5 to 2 hours before each study visit. Compliance was checked by counting the remaining pills.

### **Study design**

Subjects were measured five times: two baseline visits, with a three week interval to check for learning effects, a visit in the fifth and the 14th week of treatment to evaluate acute and chronic effects, and a visit three weeks after cessation of treatment. For each subject, all visits were scheduled at the same time of day. The drug treatment started two weeks after the second baseline visit (range one to three).

### **Outcome measures**

Primary outcome was the energy category of the Nottingham Health Profile (NHP).<sup>29</sup> Unweighted sum scores ranged from 0 (no complaints) to 100 (answered yes to all questions). Secondary outcomes included questionnaires and measurements of physical performance and muscle function.

#### *Questionnaires*

The following questionnaires were used:

- The fatigue severity scale (FSS), with a score ranging from 1 (no effect of fatigue on daily life) to 7 (severe, disabling fatigue).<sup>30</sup>
- The subjective benefit of the treatment,<sup>31</sup> with two questions: (1) “What, in your opinion, is the effect of the treatment?”, with answers ranging from 1: “very much worse”, to 7: “very much improved”; and (2) “Compared to the period before treatment, your fatigue complaints have ...?”, with answers ranging from 1: “greatly increased”, to 7: “greatly decreased”. A score of 4 indicated no change.

### *Physical performance*

Physical performance was assessed in the following ways:

- The distance walked in two minutes at comfortable speed, and maximal walking performance—the time needed to walk 75m as fast as possible.
- The duration of walking in the daily environment, measured with an ambulatory activity monitor.<sup>32</sup> The sum of walking activities (that is, continuous walking for at least five seconds) in a 48 hour recording was expressed as the percentage of the total recording time. Walking duration was measured at baseline and in the last week of the drug treatment in 24 consecutively enrolled subjects (10 pyridostigmine, 14 placebo).

### *Muscle function*

Muscle function was determined as follows:

- Maximal quadriceps strength on a chair dynamometer.<sup>a</sup> Subjects undertook three isometric maximal voluntary contractions (MVC) at an optimal knee angle with a two-minute rest interval; the greatest contraction was included in the analysis.
- Maximal voluntary activation (MVA) of the quadriceps, determined by interpolated stimulation.<sup>16</sup> Unidirectional square wave pulses of 50ms were used at a voltage of 200V.<sup>b</sup> The current was chosen such that with a 1s stimulation of 30 Hz, at least 25% of the MVC was reached. The quadriceps was stimulated for 40ms at 100 Hz at peak force during an MVC and five seconds later at rest (control tetanus). MVA was calculated from the increment in force produced by stimulation during the MVC (a) and the force due to control stimulation (b) as  $(1-a/b) \times 100$ . The highest MVA of three attempts was used for the analysis.
- Muscle fatigability of the lateral vastus, determined with surface EMG during a 30s sustained isometric contraction at 40% of the MVC that was obtained at the first baseline visit.<sup>33</sup> Muscle fatigability was quantified as the difference in the median frequency (MF) between the first five and the last five seconds ( $MF_{0-5s} - MF_{25-30s}$ ).
- Neuromuscular transmission defects (jitter) of the lateral vastus measured with single fibre electromyographic stimulation (S-SFEMG).<sup>34</sup> Measurements were done in the week of the second baseline visit and in the 14th week of the treatment period. The mean consecutive latency difference (MCD) was calculated

for 20 different muscle fibres.<sup>35</sup> Jitter was calculated as the mean MCD of the measured muscle fibres.

### Sample size and statistical analysis

With a power of 90% and a significance level of 0.05, 50 subjects would be needed to show a one item improvement on the NHP energy category.<sup>4</sup> Taking potential dropout into account, the sample size was set at 64. The primary analysis compared the subjects receiving pyridostigmine and the subjects receiving placebo with regard to changes in the outcome measures in the 14th week of treatment from the values obtained at the second baseline visit (*t* tests). The secondary analysis compared changes from baseline in the outcomes in the fifth week of treatment and three weeks after cessation of treatment between groups. The minimum clinical relevant improvement in the secondary outcome measures was set at 10%. The analyses were based on an intention to treat approach. Sub-group analyses were done for motor unit size (enlarged and normal), and for walking distance and quadriceps strength, for which sub-groups were formed on the basis of the median baseline value. All tests were two sided, and statistical significance was set at  $P < 0.05$ .

## RESULTS

Sixty seven of the 101 subjects who were screened were included (figure 1). The two groups were comparable with respect to demographic and baseline characteristics (table 1). Two subjects were excluded after treatment allocation because of thyroid dysfunction and anaemia. Two subjects withdrew from the study, one (pyridostigmine) after four weeks of treatment because of personal circumstances, and one (placebo) after six weeks of treatment because of dissatisfaction with the procedures. In general, the treatment was well tolerated. One subject (pyridostigmine) discontinued the drug because of severe diarrhoea, and was lost to follow-up for personal reasons.

**Table 1** Baseline characteristics according to treatment group

| Characteristics / outcome measures  | Pyridostigmine<br>(n=33) | Placebo<br>(n=32)     | <i>P</i> Value |
|---|--------------------------|-----------------------|----------------|
| Age (years)   | 51±8                     | 52±8                  | 0.61           |
| Gender (M/F )   | 10/23                    | 13/19                 | 0.38           |
| Age at polio onset (years)  | 3.4±4.3                  | 2.5±2.5               | 0.31           |
| Duration of PPS symptoms (years)  | 10.0±5.9                 | 10.7±6.3              | 0.64           |
| Severity of paresis of the legs (range 0-32)                                      | 24±5                     | 22±6                  | 0.14           |
| Motor unit size (mV·ms)   | 3.7±2.4 <sup>¶</sup>     | 3.9±2.5 <sup>**</sup> | 0.75           |
| Short Fatigue Questionnaire (range 1-7)   | 5.0±1.4                  | 4.8±1.2               | 0.63           |
| Nottingham Health Profile, energy category<br>(range 0-100)                       | 47±34                    | 47±36                 | 0.95           |
| Fatigue Severity Scale (range 1-7)  | 5.6±0.8                  | 5.8±1.0               | 0.38           |
| Two-minute walking distance, comfortable<br>speed (m)                             | 122±21                   | 117±27                | 0.37           |
| Maximal walking performance, 75m (s)  | 58±14                    | 64±22 <sup>††</sup>   | 0.22           |
| Walking duration (percentage of total time)                                       | 6.5±2.9 <sup>*</sup>     | 7.0±2.7 <sup>†</sup>  | 0.70           |
| Quadriceps strength (Nm)  | 90±43                    | 82±48                 | 0.51           |
| Maximal voluntary activation (range 0-100)  | 70±17 <sup>§</sup>       | 69±22 <sup>‡</sup>    | 0.94           |
| Muscle fatigability on surface EMG<br>(MF <sub>0-5s</sub> -MF <sub>25-30s</sub> ) | 1.3±2.2 <sup>¶</sup>     | 2.3±3.0 <sup>**</sup> | 0.17           |
| Neuromuscular transmission, jitter (μs)   | 40±13                    | 40±14                 | 0.90           |

With the exception of gender, values are presented as mean ± SD. Differences between the two groups were tested by *t* tests ( $\chi^2$  for gender).

\* n=9; † n=12; ‡ n=23; § n=28; ¶ n=29; \*\* n=30; †† n=31

### Compliance and blinding

Compliance was good. Fifty five of the 62 subjects who completed the study took at least 90% of their drug dose. Only two subjects (placebo) took less than 80% of their dose. The blinding code was not broken during the trial, and the blinding was successful—68% of the subjects receiving pyridostigmine and 47% of the subjects receiving placebo guessed their actual treatment correctly (*P*=0.37). The investigator

guessed correctly for 39% of the pyridostigmine-treated subjects and for 42% of the placebo-treated subjects ( $P=0.20$ ).

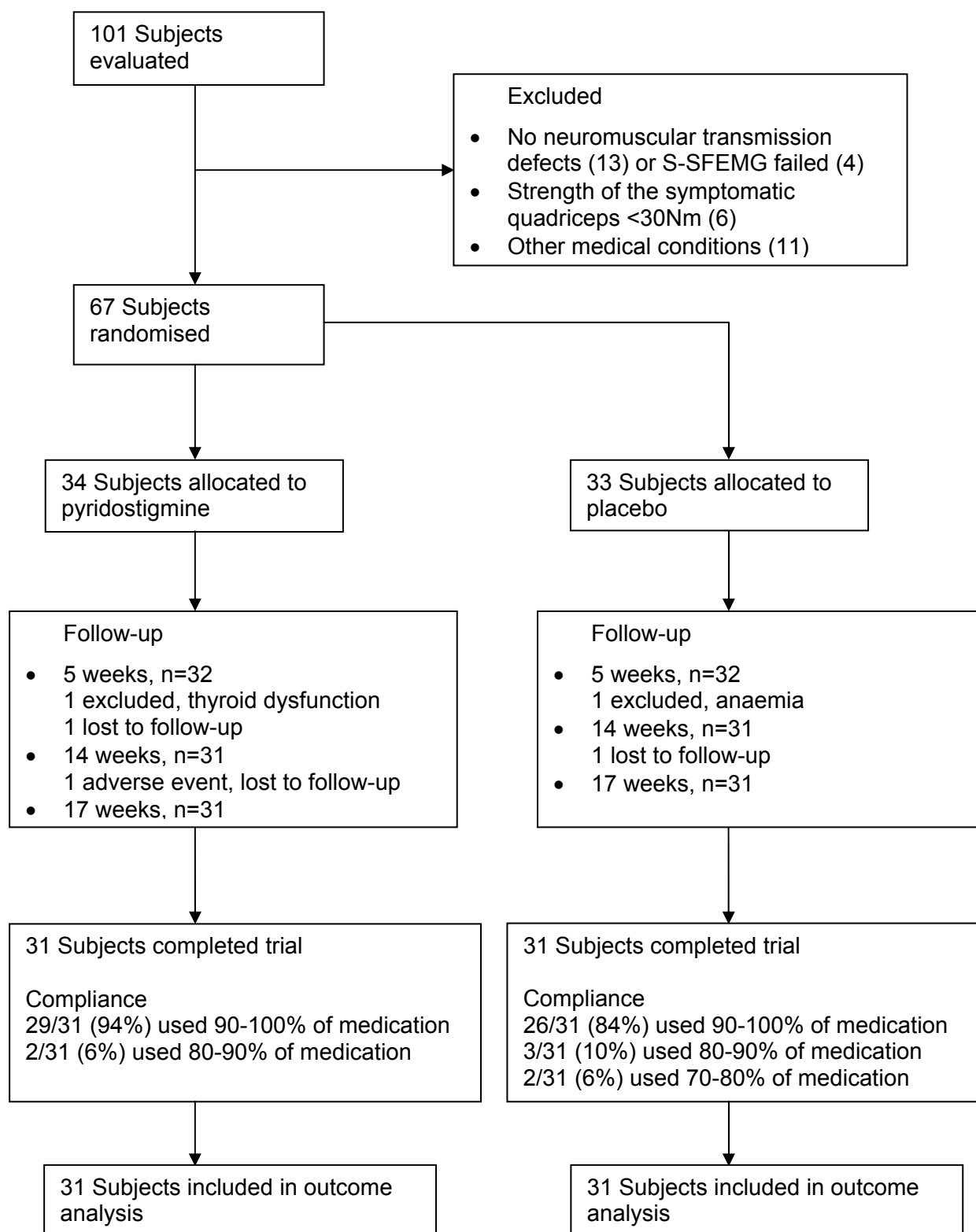
## Outcome

There was no significant difference in change on the primary outcome NHP energy category between the two groups during the treatment period (table 2). In the 14th week of treatment, a significant reduction of 36% was found in both groups. No difference in change on the FSS or in the subjective benefit of the treatment was found between the two groups; both improved significantly during the treatment period.

In the 14th week of treatment, the walking distance improved more in the pyridostigmine group than in the placebo group (by 7.2m (6.0%);  $P=0.003$ ). No effect of pyridostigmine was found on maximal walking performance. Three weeks after the treatment period the pyridostigmine group improved significantly more than the placebo group on walking distance and maximal walking performance. No difference in change in the duration of walking was found between the two groups. Walking duration increased significantly in the pyridostigmine group.

There was no difference in change in quadriceps strength between the two groups. In the 14th week of treatment, significant improvements were found in both groups. In the last week of treatment, 58% of the subjects in the pyridostigmine group improved on both quadriceps strength and walking distance, whereas 13% of the subjects in this group did not improve on either of these outcome measures ( $P<0.05$ ,  $\chi^2$  test). In the placebo group, 32% improved on both outcome measures, whereas 19% did not ( $P=1.00$ ).

In 24 subjects (10 pyridostigmine, 14 placebo), MVA could not be measured owing to inability to stimulate the quadriceps to exert at least 25% of the MVC ( $n=21$ ) or because of intolerance of the measurement ( $n=3$ ). In the fifth week of treatment and three weeks after the treatment period, MVA had improved significantly more in the pyridostigmine group than in the placebo group.



**Figure 1** Flow diagram. The number of subjects measured at the study visits during the trial and the compliance with the study drug in the two groups.

Data on muscle fatigability were missing for seven subjects in both the pyridostigmine and the placebo groups owing to recording artefacts. Muscle fatigability did not change in either group.

Jitter values were missing for three subjects in the placebo group (intolerance in two, technical failure in one) in the last week of treatment. No difference in change in jitter was found between the two groups.

### **Sub-group analyses**

Motor unit size was missing in four subjects (three pyridostigmine, one placebo) owing to technical failures. Motor unit size was increased in 23 subjects (12 pyridostigmine, 11 placebo) and was normal in 35 subjects (16 pyridostigmine, 19 placebo). For the subjects with enlarged motor units, no difference in change between the two groups was found for any outcome measure. For the subjects with normal sized motor units, walking distance improved 9.5m more (8.4%;  $P=0.002$ ), and maximal walking performance 2.9s more (4.5%;  $P=0.03$ ) in the pyridostigmine group than in the placebo group. No differences in effects were found for sub-groups based on walking distance or quadriceps strength.

## **DISCUSSION**

Our study provided no evidence of any benefit of pyridostigmine in reducing fatigue in patients with postpoliomyelitis syndrome with increased fatigue and neuromuscular transmission defects in a quadriceps muscle with new neuromuscular symptoms. The only significant difference in change between the two study groups in the 14th week of treatment was for walking distance, though the improvement of 6% was less than considered clinically relevant.

The main question to be answered is whether pyridostigmine is indeed ineffective as a treatment for postpoliomyelitis syndrome, or whether the negative result reflects shortcomings of the study.



**Table 2** Changes in outcome measures from the second baseline measurements at five and 14 weeks of treatment and three weeks after the end of treatment, according to treatment group

|   | Week 5 of treatment                          |  |                              | Week 14 of treatment                         |   |                              | Three weeks after the end of treatment       |   |                              |
|---|--|--|------------------------------|--|---|------------------------------|--|---|------------------------------|
|   | Pyridostigmine<br>(n=31)                     | Placebo<br>(n=31)                            | $\Delta$ (95% CI)<br>P value | Pyridostigmine<br>(n=31)                     | Placebo<br>(n=31)                             | $\Delta$ (95% CI)<br>P value | Pyridostigmine<br>(n=31)                     | Placebo<br>(n=31)                           | $\Delta$ (95% CI)<br>P value |
| Nottingham Health Profile energy cat. (range 0-100)             | -10.8 $\pm$ 35.9<br>P=0.11                   | -10.8 $\pm$ 26.4<br>P=0.03                   | 0.0 (16.0 to -16.0)<br>1.00  | -18.3 $\pm$ 36.4<br>P=0.01                   | -17.2 $\pm$ 33.2<br>P=0.01                    | -1.1 (-18.8 to 16.6)<br>0.90 | -6.5 $\pm$ 37.9<br>P=0.35                    | -8.6 $\pm$ 25.8<br>P=0.07                   | 2.2 (-14.3 to 18.6)<br>0.80  |
| Fatigue Severity Scale (range 1-7)                              | -0.2 $\pm$ 0.7<br>P=0.07                     | -0.4 $\pm$ 0.5<br>P<0.01                     | 0.1 (-0.2 to 0.4)<br>0.44    | -0.6 $\pm$ 0.9<br>P<0.01                     | -0.4 $\pm$ 0.9<br>P=0.01                      | -0.2 (-0.6 to 0.3)<br>0.48   | -0.5 $\pm$ 1.0<br>P<0.01                     | -0.4 $\pm$ 0.6<br>P<0.01                    | -0.1 (-0.6 to 0.3)<br>0.48   |
| Subjective benefit of treatment                                 | 0.5 $\pm$ 0.7<br>P<0.01                      | 0.5 $\pm$ 0.8<br>P<0.001                     | -0.1 (-0.5 to 0.3)<br>0.61   | 0.5 $\pm$ 0.9<br>P=0.01                      | 0.5 $\pm$ 0.9<br>P<0.01                       | -0.1 (-0.5 to 0.4)<br>0.78   |  |   |                              |
| Question 1  |  |  |                              |  |   |                              |  |   |                              |
| Question 2  |  |  |                              |  |   |                              |  |   |                              |
| Two-minute walking distance (m)                                 | 8.6 $\pm$ 9.9 $^{\S\S}$<br>P<0.001           | 5.8 $\pm$ 5.9<br>P<0.001                     | 2.8 (-1.4 to 7.0)<br>0.18    | 10.2 $\pm$ 9.4<br>P<0.001                    | 3.0 $\pm$ 8.8<br>P=0.07                       | 7.2 (2.6 to 11.9)<br>0.003   | 12.7 $\pm$ 9.3<br>P<0.001                    | 6.0 $\pm$ 9.6<br>P<0.01                     | 6.8 (2.0 to 11.6)<br>0.01    |
| Maximal walking performance, 75m (s)                            | -1.1 $\pm$ 3.5<br>P=0.09                     | 0.5 $\pm$ 5.8 $^{\S\S}$<br>P=0.76            | -1.5 (-4.0 to 0.9)<br>0.21   | -1.6 $\pm$ 4.4<br>P=0.06                     | 0.1 $\pm$ 4.0 $^{\dagger\dagger}$<br>P=0.89   | -1.7 (-3.9 to 0.5)<br>0.13   | -1.9 $\pm$ 4.1 $^{\dagger\dagger}$<br>P=0.02 | 0.6 $\pm$ 4.4 $^{\S\S}$<br>P=0.62           | -2.6 (-4.8 to -0.3)<br>0.03  |
| Duration of walking (% of total time)                           |  |  |                              | 1.5 $\pm$ 1.3 $^{\dagger}$<br>P<0.01         | 1.0 $\pm$ 1.7 $^*$<br>P=0.12                  | 0.5 (-0.8 to 1.9)<br>0.42    |  |   |                              |
| Quadriceps strength (Nm)  | 6.7 $\pm$ 13.7<br>P=0.01                     | 5.0 $\pm$ 13.9<br>P=0.06                     | 1.7 (-5.3 to 8.7)<br>0.63    | 12.7 $\pm$ 21.4<br>P<0.01                    | 6.0 $\pm$ 13.4<br>P=0.02                      | 6.7 (-2.4 to 15.7)<br>0.15   | 5.1 $\pm$ 19.0<br>P=0.14                     | 3.7 $\pm$ 12.1<br>P=0.10                    | 1.5 (-6.6 to 9.5)<br>0.72    |
| Maximal voluntary activation (range 0-100)                      | 6.5 $\pm$ 14.3 $^{\dagger\dagger}$<br>P=0.04 | -4.7 $\pm$ 11.3 $^{\dagger}$<br>P=0.09       | 11.1 (3.0 to 19.3)<br>0.01   | 7.7 $\pm$ 14.2 $^{\dagger\dagger}$<br>P=0.02 | 1.1 $\pm$ 14.2 $^{\dagger}$<br>P=0.74         | 6.6 (-2.2 to 15.5)<br>0.14   | 5.8 $\pm$ 13.2 $^{**}$<br>P=0.03             | -3.3 $\pm$ 12.7 $^{\S}$<br>P=0.26           | 9.1 (1.3 to 16.8)<br>0.02    |
| Muscle fatigability (MF <sub>0-5s</sub> -MF <sub>25-30s</sub> ) | 0.1 $\pm$ 2.9 $^{**}$<br>P=0.82              | -0.0 $\pm$ 3.5 $^{\dagger\dagger}$<br>P=0.96 | 0.2 (-1.6 to 1.9)<br>0.85    | 0.9 $\pm$ 3.4 $^{**}$<br>P=0.18              | 0.2 $\pm$ 3.3 $^{**}$<br>P=0.80               | 0.7 (-1.1 to 2.6)<br>0.43    | 0.9 $\pm$ 3.1 $^{**}$<br>P=0.17              | 0.4 $\pm$ 4.0 $^{\dagger\dagger}$<br>P=0.58 | 0.4 (-1.5 to 2.4)<br>0.66    |
| Neuromuscular transmission, jitter ( $\mu$ s)                   |  |  |                              | -5.6 $\pm$ 16.0<br>P=0.06                    | -2.8 $\pm$ 21.1 $^{\dagger\dagger}$<br>P=0.49 | -2.8 (-12.5 to 6.9)<br>0.57  |  |   |                              |

Change is calculated as the scores at or after intervention minus the scores at baseline and is presented as mean  $\pm$  SD. The difference in change between groups ( $\Delta$ ) is calculated from the change in the pyridostigmine group minus the change in the placebo group and is presented as mean difference (95% confidence interval) and the P value of the *t* test. n=9;  $^*$ n=12;  $^{\dagger}$ n=19;  $^{\S}$ n=20;  $^{**}$ n=23;  $^{\dagger\dagger}$ n=28;  $^{\S\S}$ n=29;  $^{\dagger\dagger\dagger}$ n=30 CI, confidence interval; MF, median frequency.

### **Was the dose of pyridostigmine adequate?**

Taking into account the negative result of a randomised controlled trial with 180 mg a day,<sup>19</sup> we increased the dose of pyridostigmine to 240 mg. To assess whether this dose was pharmacologically effective, changes in neuromuscular transmission defects were monitored (S-SFEMG). The fact that no significant improvement in neuromuscular transmission was found in the pyridostigmine group might suggest that the dose of 240 mg was not adequate. However, the large standard deviation of the difference in jitter found in the placebo group (table 2), probably caused by large variation in neuromuscular transmission defects between end-plates, indicates that the reproducibility of jitter was poor. Thus jitter was not an appropriate measure to establish the effectiveness of the pyridostigmine dose. Nonetheless, plasma concentrations of pyridostigmine can vary greatly between individuals,<sup>36</sup> and the dose may have been insufficient for an unknown number of subjects. This implies that individual adjustment may be required to obtain an effective dose.

### **Was the ability to detect an effect of pyridostigmine adequate?**

The sample size of the study population was calculated with an expected standard deviation of 30 in the change in NHP energy category score.<sup>4</sup> The NHP energy category scores which were obtained were in agreement with this assumption and confirmed an adequate power calculation. However, the NHP energy category showed a substantial ceiling effect at baseline, where 15 subjects (23%) had a score of 0. In addition, the NHP energy category scores in the placebo group decreased significantly during the treatment period. To demonstrate a beneficial effect of pyridostigmine, the scores in the pyridostigmine group would have to decrease by more than 33%, which was only found possible in 15 subjects.

Fatigue was also measured with the FSS, which has more response choices and showed no ceiling effect. As the FSS also failed to improve with pyridostigmine, the lack of effect on the NHP energy category cannot be attributed to an insufficient ability to detect change.

### **Does pyridostigmine have an effect on muscle function?**

In this study, many comparisons were made and statistically tested. By chance, multiple testing can yield significant differences that do not reflect true differences and may produce misleading results.<sup>37</sup> Some of the significant differences found—for instance, on maximal walking performance and MVA three weeks after treatment—may therefore be coincidental. However, if these differences had resulted from chance alone, they would have been equally distributed over the two treatment groups. The significant improvements in walking distance, the duration of walking, quadriceps strength, and MVA were all in favour of the pyridostigmine group. These findings suggest that pyridostigmine does improve muscle function to some extent. This is also supported by the significant association between the improvement in walking performance and the improvement in quadriceps strength, which was found in the pyridostigmine group but not in the placebo group.

It was expected that pyridostigmine would slow down muscle fatigability. However, no changes were found on the surface EMG during the treatment period in either of the two groups. The protocol used, with a sustained contraction at 40% of MVC (as obtained at baseline), did not induce high levels of fatigue, as was shown by the small decline in median frequency at baseline. This left little opportunity for improvement, and a relatively higher level of effort might have been more appropriate.

### **Do subjects with normal sized motor units benefit more from pyridostigmine?**

It was hypothesised in advance that subjects with enlarged motor units would benefit most from pyridostigmine.<sup>9,15</sup> Contrary to this expectation, subjects with normal sized motor units improved in walking performance, while those with enlarged motor units did not. Although this unexpected sub-group effect must be interpreted with caution, it should be realised that all quadriceps muscles were symptomatic, and all showed abnormal neuromuscular transmission. An explanation might be that the normal sized motor units were, in fact, enlarged motor units that had become reduced in size over time owing to the distal degeneration of axonal branches.<sup>12,38,39</sup>

## CONCLUSIONS

The result of this trial was negative, as pyridostigmine did not reduce fatigue in a selected group of subjects with postpoliomyelitis syndrome who were most likely to benefit from this treatment. On the other hand, the significant effect of pyridostigmine on walking distance—together with some effects on walking duration, quadriceps strength, and maximal voluntary activation—suggest that pyridostigmine may improve muscle function. The effect of pyridostigmine might be related to the size of the motor units with neuromuscular transmission defects. In subjects with normal sized motor units, the effect size might be of relevance. However, a confirmatory study is needed as this finding resulted from a sub-group analysis that was not prespecified.

Because no effect was found on perceived fatigue, future studies should concentrate on the effects of individually adjusted doses of pyridostigmine on physical performance in subjects with postpoliomyelitis syndrome.

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## Suppliers

- <sup>a</sup> Kinetic Communicator; Chattecx Corp, Chattanooga Group, 4717 Adams Rd, Hixson, TN 37343.
- <sup>b</sup> DS7A; Digitimer Ltd, Welwyn Garden City, Hertfordshire, England.





## CHAPTER 7

Walking in postpoliomyelitis syndrome:  
the relationships between time-scored tests,  
walking in daily life and perceived mobility problems

Herwin Horemans, Hans Bussmann, Anita Beelen,  
Henk Stam and Frans Nollet

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## ABSTRACT

**Objective:** To compare walking test results with walking in daily life, and to investigate the relationships between walking tests, walking activity in daily life, and perceived mobility problems in patients with postpoliomyelitis syndrome.

**Subjects:** Twenty-four ambulant patients with postpoliomyelitis syndrome.

**Methods:** Walking tests were performed at self-preferred and maximal speed. Walking activity was measured with an ambulatory activity monitor. Heart rate, step cadence and walking speed in the test and in daily life were compared. Walking speed in daily life was represented by the intensity of walking. Perceived mobility problems were assessed with the Nottingham Health Profile.

**Results:** Heart rate during walking was lower in the test at self-preferred speed than in daily life (mean difference:  $11.3 \pm 10.4$ ;  $P=0.001$ ). Self-preferred walking speed in the test and in daily life correlated significantly ( $r=0.55$ ;  $P=0.04$ ). In a sub-group with a test performance below the median value, test performance correlated significantly with walking activity. No significant correlation was found between perceived mobility problems and walking activity.

**Conclusion:** Walking in daily life may be more demanding than walking under standardized conditions. Patients with postpoliomyelitis syndrome with the lowest test performance walked less in daily life. Patients do not necessarily match their activity pattern to their perceived mobility problems.

Paralytic poliomyelitis most often affects the muscles of the lower extremities. As a consequence, many individuals with late onset polio sequelae report a decline in walking ability.<sup>1,2</sup> Limitation in walking activity is one of the most prominent problems of patients with postpoliomyelitis syndrome (PPS).<sup>3-5</sup>

Walking capacity has been reported as an indicator of performance and activities of daily living (ADL) activity in patients with PPS.<sup>4,6-9</sup> Frequently used methods to measure walking performance are time-scored tests at maximal or selfpreferred walking speed, usually carried out in a clinical setting.<sup>4,7,8</sup> These standardized performance tests measure various aspects of walking, such as speed, distance and physical effort.

Walking at comfortable speed in a clinical setting is assumed to represent walking in daily life.<sup>10,11</sup> However, the level of effort and the characteristics of walking, such as speed and step cadence, during walking tests under standardized conditions may differ from those of walking in daily life, when conditions are not standardized.

Therapeutic interventions for polio patients may aim at increasing their walking ability. It can be questioned whether walking ability in daily life, and changes in it, can be measured with walking tests. It seems likely that a relationship exists between walking test performance and the amount of walking in daily life.<sup>12</sup> However, this relationship has never been investigated in patients with PPS. We hypothesized that walking test performance is an indicator of the amount of walking in daily life.

In patients with PPS, perceived physical mobility problems were found to be related to performance in walking tests.<sup>4</sup> However, it is unknown whether perceived mobility problems also imply that there is less actual walking activity. Therefore, it is important to investigate the relationship between perceived physical mobility problems and actual walking in daily life.

Recently, we carried out a study to investigate the effects of pyridostigmine on fatigue in PPS patients.<sup>13</sup> In that study, walking tests were performed at self-preferred and maximal speed, and the amount of walking in daily life was measured with an activity monitor.<sup>14</sup> The activity monitor allows longterm (48 hours) continuous measurement of daily activities and physical effort with minimal influence on behaviour. Perceived

physical mobility problems were also measured in this study with a validated questionnaire.

The purpose of the present study was threefold: (1) to investigate whether walking at self-preferred speed in a clinical setting reflects the levels of effort and characteristics of normal walking in the actual circumstances of daily life; (2) to investigate whether the performance in walking tests is related to the amount of walking in daily life; and (3) to investigate the relationship between perceived physical mobility problems and the amount of walking in daily life.

## METHODS

The data were derived from the measurements of 24 patients with PPS (4 men and 20 women) who were consecutively included in the pyridostigmine trial, who underwent ambulatory monitoring of their daily life activities.<sup>13</sup> The mean age  $\pm$  SD of these patients was  $54.5 \pm 8.9$  years. PPS symptoms had existed for an average of  $10.9 \pm 7.7$  years, and all patients had new muscle weakness in at least 1 leg. All patients were able to walk for at least 2 minutes at self-preferred speed. Walking aids and orthopaedic devices were used in the walking tests in the same way in which they were used when walking outdoors. Nine patients used some type of walking aid (canes, crutches, orthosis).

### Outcome measures

#### *Walking tests*

Two tests were performed on a closed, marked 65-metre indoor, oval-shaped track. The patients first walked for 2 minutes at self-preferred speed and the distance was measured. They then walked 75 metres at maximal speed (without running) and the time was recorded. Each test was started after the patient had rested for 5 minutes, sitting on a chair. For each test, the mean walking speed was calculated from the distance and the time. When walking at self-preferred speed, the patient's heart rate was measured every 5 seconds with a Polar Sporttester.<sup>a</sup> Mean steady state heart rate was calculated from the recording period between 70 and 90 seconds after the patient had started walking.

When walking at self-preferred speed, a unilateral surface electromyography (EMG) of the patient's quadriceps muscles was recorded with a portable ME300 Muscle Tester.<sup>b</sup> Disposable surface electrodes (Medi-Trace Pellet, self-adhesive Ag/AgCl ECG electrodes; surface: 1cm<sup>2</sup>, centre-to-centre distance: 31mm) were placed over the vastus lateralis. Over the same period that was used to calculate the mean heart rate, the step cadence was determined from the peak amplitudes in the EMG signal.<sup>15</sup>

### *Walking in daily life*

The activity monitor,<sup>c</sup> described in detail by Bussmann et al.,<sup>14</sup> is based on long-term accelerometry. Signals from piezo-resistive accelerometers attached to the thighs and trunk were continuously measured and stored (32 Hz) on a portable data-recorder. Data from ECG were recorded simultaneously. The patients' data were recorded for a period of 48 hours in their regular daily life environment. After downloading the stored data onto a computer, several body postures and motions (walking included) were automatically detected from the accelerometer signals. The duration of walking was calculated as the percentage of time that a patient demonstrated walking activity (defined as walking for at least 5 seconds) in the 48-hour recording period. In addition, 'longer walking' was determined as the duration of walking continuously for at least 30 seconds, and was expressed as a percentage of the 48 hours.

Four walking periods of at least 120 seconds were selected to determine steady state heart rate, step cadence and motility (which is an indicator of walking speed). Patients had not performed strenuous activities in the 60 seconds before the start of these walking periods. The time-span between 2 periods was a minimum of 60 minutes. Values were calculated from the recording interval between 70 and 90 seconds after the onset of walking, and were averaged over the 4 walking periods.

Heart rate was extracted from electrocardiographic data,<sup>16</sup> and cadence was extracted from the pattern of the accelerometry data recorded from the thighs. Motility expresses the intensity of the accelerometry data. Its value depends on the variability of the accelerometer signal around the mean, i.e. the amplitudes of the peaks and the frequency of occurrence of these peaks.<sup>14</sup> It has been shown that a strong

relationship exists between motility and walking speed, and that this relationship is independent of the efficiency of walking.<sup>16,17</sup>

#### *Perceived physical mobility problems*

Perceived mobility problems were assessed with the “physical mobility” category of a validated Dutch version of the Nottingham Health Profile (NHP).<sup>18</sup> The score on the NHP physical mobility category was calculated as the percentage of the 8 items answered with “yes” (a perceived problem).

The walking tests were performed and the NHP was administered during the second pre-medication study visit to the hospital.<sup>13</sup> Within 7 days after the hospital visit, walking in daily life was measured with the activity monitor.

#### **Statistics**

Walking test results and walking in daily life were compared with respect to heart rate, cadence and walking speed, by means of *t* tests or Pearson’s correlation coefficient. The within-subject variability of heart rate, cadence and motility during walking in daily life over the 4 periods was determined with the coefficient of variation,<sup>19</sup> calculated as:

$$\left( \sum_{\text{subject}=i..n} \frac{\sigma(p_i)}{p_i} \bullet 100 \right) / n$$
, with  $\sigma(p_i)$  as the standard deviation and  $\overline{p_i}$  as the mean of the 4 periods of subject *i*, and *n* as the total number of subjects.

The relationships between walking speed in the walking tests and the duration of walking and the duration of longer walking in daily life were analysed by calculating Pearson’s correlation coefficients. Relationships were studied for all patients, and for sub-groups, based on the median value of the walking test results, i.e. patients with a walking performance below the group median value and patients with a walking performance above the group median value.

Relationships between perceived physical mobility problems and walking in daily life and walking test results were analysed by calculating Spearman’s correlation coefficients. The significance level was set at  $P < 0.05$ . Statistical analysis was performed with the SPSS 10.0.5 software package<sup>d</sup>.

## RESULTS

For the test at self-preferred speed, the mean walking speed was  $1.02 \pm 0.17 \text{ m/s}$ , which was significantly lower ( $P < 0.01$ ) than the walking speed of  $1.32 \pm 0.24 \text{ m/s}$  in the maximal test (mean difference:  $0.31 \pm 0.16$ ; 95%CI:  $0.24-0.37$ ). Walking at self-preferred and maximal speed correlated significantly ( $r = 0.75$ ,  $P < 0.01$ ). For walking in daily life, the correlation between the duration of walking (6.6%) and the duration of longer walking (2.9%) was  $r = 0.89$  ( $P < 0.01$ ).

Only 14 patients had walked at least 4 periods with a minimal duration of 120 seconds. The coefficient of variation  $\pm$  SD over these 4 periods was  $5.1 \pm 2.0\%$  for heart rate,  $3.0 \pm 1.9\%$  for cadence and  $7.8 \pm 2.5\%$  for motility.

### Characteristics of walking in the test at self-preferred speed compared with walking in daily life

The mean heart rate in the walking test at self-preferred speed was significantly lower than when walking in daily life ( $P < 0.01$ ) (table 1). There was no difference between the cadence in the walking test and the cadence when walking in daily life. The correlation between cadence in the test and in daily life was  $r = 0.46$  (n.s.). The correlation between walking speed in the test and motility of walking in daily life was  $r = 0.55$  ( $P = 0.04$ ).

### Relationship between walking test performance and the duration of walking in daily life

Both self-preferred and maximal speed in the walking tests correlated significantly with the duration of walking and longer walking in daily life (table 2). The strongest correlation was found between self-preferred speed and walking duration ( $r = 0.52$ ,  $P < 0.01$ ).

For the sub-group with walking test results below the median value of the total group, significant correlations were found between walking test performance and walking activity in daily life. No significant correlations between walking test performance and walking activity in daily life were found for the sub-group with the better test performance results.



**Table 1** Results of the walking test at self-preferred speed and walking in daily life

|                                      | Walking test at<br>self-preferred speed | Walking in<br>daily life | Mean difference | 95% CI;<br><i>P</i> value   |
|--------------------------------------|---|--------------------------|-----------------|-----------------------------|
| N=24                                 |   |                          |                 |                             |
| Speed (m/s)                          | 1.02±0.17                               |                          |                 |                             |
| Duration of walking<br>(% time)      |   | 6.6±2.7                  |                 |                             |
| Duration of walking<br>>30s (% time) |   | 2.9±1.7                  |                 |                             |
| N=14                                 |   |                          |                 |                             |
| Heart rate (beats/min)               | 98.6±9.2                                | 110.0±14.0               | 11.3±10.4       | 5.4-17.3;<br><i>P</i> <0.01 |
| Cadence (steps/min)                  | 107.6±10.0                              | 109.1±6.6                | 1.5±9.1         | -3.8-6.8;<br><i>P</i> =0.55 |
| Speed (m/s)                          | 1.08±0.14                               |                          |                 |                             |
| Motility (g)                         |   | 0.23±0.03                |                 |                             |

The means ± SD are given for the outcome measures.

One g is 9.8 ms<sup>-2</sup>.

### Relationship between perceived physical mobility problems and walking activity in daily life

The median (25-75 percentile) score on the NHP physical mobility category was 25 (16-50). The NHP physical mobility category correlated with the walking test performance for both self-preferred and maximal speed (table 3). The NHP physical mobility category did not correlate with the duration of walking or with longer walking in daily life.

**Table 2** Relationship between walking test performance and the duration of walking in daily life

| Walking test performance    | Walking in daily life |                       |
|-----------------------------|-----------------------|-----------------------|
|                             | Walking duration      | Walking duration >30s |
| Self-preferred speed (n=24) | 0.52**                | 0.50*                 |
| sub-group low speed         | 0.65*                 | 0.59*                 |
| sub-group high speed        | -0.27*                | -0.24                 |
| Maximal speed (n=24)        | 0.42*                 | 0.46*                 |
| sub-group low speed         | 0.73**                | 0.81**                |
| sub-group high speed        | 0.27                  | 0.60*                 |

Pearson's correlation coefficients are presented. Sub-groups were formed, based on the median value of the walking test results. Median values for self-preferred speed and maximal speed were respectively 1.05m/s and 1.29m/s.

\**P* level below 0.05; \*\**P* level below 0.01.

## DISCUSSION

The aim of the present study was to investigate the relationships between clinical walking tests, walking in daily life and perceived physical mobility problems in patients with PPS. Specifically patients with PPS were studied because they demonstrate an increase in neuromuscular symptoms and perceive a decline in walking ability.<sup>4,10</sup>

It appeared that walking in daily life differed from walking under standardized conditions: the heart rate was significantly higher in daily life than in a test at self-selected speed. This may be due to the less straining conditions during the walking test: the walking surface is flat and level, no additional tasks have to be performed, and there are no weather influences. This is in contrast with a study in patients with chronic obstructive pulmonary disease, in which no difference was found in walking speed and heart rate between an indoor and outdoor 6-minute walking test.<sup>20</sup>

However, the outdoor test in that study was performed under optimal conditions (a flat sidewalk in a quiet neighbourhood) and no additional tasks were carried out.

The higher heart rate in daily life in the present study may also be due to carry-over effects from previous activities. Although the walking periods from which the heart rate was determined with the activity monitor were all preceded by a period of relative rest, the walking tests were always preceded by a standardized period of absolute rest (5 minutes of sitting on a chair).

**Table 3** Relationship between perceived physical mobility problems, and duration of walking in daily life and walking test performance (n=24)

|                          | NHP physical mobility category |
|--------------------------|--------------------------------|
| Walking in daily life    |                                |
| Walking duration         | -0.29                          |
| Walking duration >30s    | -0.15                          |
| Walking test performance |                                |
| Self-preferred speed     | -0.70**                        |
| Maximal speed            | -0.69**                        |

Spearman's correlation coefficients are presented.

\*  $P < 0.05$ ; \*\*  $P < 0.01$ .

In contrast with heart rate, no systematic difference was found between cadence in the walking test at self-preferred speed and cadence when walking in daily life. However, the large standard deviation of the mean difference and the lack of correlation between the cadence in the walking test and in daily life indicate large within-subject variability between the 2 conditions. The small coefficient of variation (3%) for cadence in daily life suggests that this is not due to large within-subject variability of walking in daily life. It seems that the individual cadence when walking in the test differs from cadence when walking in daily life, but in different directions among patients. The cause of this remains speculative.

Both self-preferred walking speed and maximal walking speed were comparable to what has been found in an earlier study focusing on patients with PPS.<sup>21</sup> The walking speed of patients with PPS is noticeably lower than that of healthy subjects.<sup>22</sup> The percentage of walking activity in daily life of patients with PPS (6.6%) has also been found to be less than that of healthy subjects (9.1%), but higher than that of patients with chronic congestive heart failure (3.4%).<sup>23</sup>

In the present study, significant relationships were found between walking test performance and the amount of walking in daily life. However, walking performance at self-preferred speed explained only 27% ( $r^2=0.52^2$ ; table 2) of the variance in duration of walking in daily life. This illustrates that actual walking in daily life is not only determined by walking ability. It is likely that daily life behaviour is largely determined by social behaviour, personal lifestyle, working conditions and living circumstances, such as the localization of shops, etc. Interestingly, much stronger relationships between walking test performance and walking in daily life were found for those patients with PPS with lower walking ability in the tests. Apparently, actual walking behaviour in these patients is mainly determined by their reduced walking ability. This is best illustrated by the variance in longer walking duration (>30 seconds) that is explained for 66% ( $r^2=0.81^2$ ; table 2) by the performance in the maximal walking test. Maximal walking speed is apparently a better indicator of capacity than self-preferred walking speed for prolonged walking.

One limitation of measuring behaviour is the day-to-day variability in daily life activities.<sup>23</sup> Single-day measurements are probably not representative for a “general” level of daily activities. An attempt was made to take this into account by measuring for a period of 48 hours. However, it is still possible that variability between days may have affected some of the relationships found in this study.

Both self-preferred and maximal speed in the walking tests were significantly related to perceived physical mobility problems. This is in agreement with the results of a study carried out by Nollet et al. in a different group of polio patients.<sup>4</sup> Surprisingly, no significant relationships were found between perceived physical mobility problems and walking duration in daily life. This is in line with the results of a study carried out

by Willen et al., who found no significant relationship between the score on the Physical Activity Scale for the Elderly and the score on the NHP physical mobility category in patients with PPS.<sup>10</sup> The lack of correlation between perceived physical mobility problems and walking in daily life might reflect the fact that certain tasks simply have to be performed in daily life, despite perceived limitations in physical performance. It is well known that patients with PPS tend to ignore or even deny their disabilities.<sup>24</sup>

## CONCLUSIONS

In conclusion, the cardiac response of patients with PPS during walking in daily life was significantly higher than during walking in test circumstances. It may be that walking tests at self-preferred speed tend to under-estimate the physical effort of walking in daily life. Test performance was related to walking in daily life, and this relationship was most pronounced for those with the lowest test performance. Apparently, the limited capacity of these patients largely determined their physical behaviour. Although perceived physical mobility problems were related to walking test performance, they were not related to walking behaviour in daily life. This indicates that patients with PPS do not necessarily adapt their behaviour to their perceived capacities. Ambulatory monitoring of daily activities may be helpful in future studies that focus on changing actual behaviour in daily life.

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## Suppliers

- <sup>a</sup> Polar Vantage NV with Advantage Interface System; Polar Electro Nederland BV, Almere, The Netherlands
- <sup>b</sup> ME300 Muscle Tester, 2- channel; Mega Electronics Ltd., Kuopio, Finland
- <sup>c</sup> RAM, Temec Instruments BV, Kerkrade, The Netherlands
- <sup>d</sup> SPSS Inc., Chicago, Illinois, USA



## CHAPTER 8

General discussion







The previous chapters of this thesis described the results of the randomised clinical trial (RCT) that was carried out to investigate the effects of pyridostigmine on fatigue, physical performance and muscle function in patients with postpoliomyelitis syndrome (PPS), and focused on the validity and reproducibility of the main outcome measures used in our trial. In the present chapter the methodology and the outcome of the trial are evaluated, the clinical implications are discussed, and some recommendations are made for future research.

## Methodological considerations

The RCT described in this thesis was conducted to test the hypothesis that pyridostigmine reduces fatigue in patients with PPS. During the design of the trial we were informed by Trojan and colleagues about the results of their multicenter trial on pyridostigmine which they were about to publish.<sup>1</sup> This gave us the opportunity to reflect on the methodology of our study and to include some of their suggestions concerning the design and the choice of outcome measures. It resulted in the incorporation of more specific outcome measures for fatigue and functional performance, the prescription of a higher dosage of pyridostigmine, and the selection of patients with PPS who were more likely to respond to pyridostigmine, namely those PPS patients with severe fatigue and with neuromuscular transmission defects, as demonstrated by stimulation single fibre electromyography (S-SFEMG). However, in our study we found no beneficial effect of pyridostigmine in these selected PPS patients. Only a limited and clinically non-relevant improvement in walking performance was found. There may be several reasons for these negative results.

First, they could be due to methodological limitations. The primary outcome measure, the Nottingham Health Profile energy category, showed a severe ceiling effect, and all the questionnaires showed only moderate reproducibility.<sup>2</sup> However, these limitations do not explain the negative results, since no effect was found on the other fatigue scores (such as the Fatigue Severity Scale), and because the mean changes on the fatigue outcomes were small.<sup>3</sup> A recent study reported no difference in decline of frequency of the EMG signal during sustained contractions between the symptomatic muscles of patients with PPS and the muscles of healthy controls.<sup>4</sup> This

implies that determining muscle fatigue by the rate of decline in median frequency may not be appropriate in patients with PPS.

Secondly, the significant but clinically non-relevant improvement in walking performance may be due to an insufficient dosage of pyridostigmine for some patients. Unfortunately, this could not be determined with certainty because the S-SFEMG measurements that were used to assess the effectiveness of pyridostigmine were rather variable, probably due to a wide variation in neuromuscular transmission defects between end-plates.

Another explanation might be that our trial was based on the wrong assumption. We assumed that the increased fatigue in patients with PPS was due to increased muscle fatigability, caused by neuromuscular transmission defects. We hypothesized that pyridostigmine would improve neuromuscular transmission, and thereby muscle function, and would eventually reduce fatigue. However, increased neuromuscular transmission defects may only be one of the possible causes of fatigue in PPS. Defects in the neuromuscular transmission are present but not always observed in post-polio subjects with a reduction in muscle strength and increased fatigability.<sup>4</sup> It has been found that there can be several other causes of fatigue in patients with PPS, such as impaired calcium kinetics (leading to disturbances in excitation contraction coupling of the actine and myosine filaments),<sup>5</sup> decreased capillary density and oxidative and glycolytic enzyme potentials,<sup>6</sup> impaired voluntary muscle activation (that can be due to impaired reflex mechanism),<sup>7,8</sup> degeneration of neurons of the reticular formation and basal ganglia,<sup>9</sup> chronic pain, respiratory dysfunction, and sleep disorders.<sup>10</sup> Therefore, it is conceivable that transmission failures, although present, may not have been the primary cause of fatigue in an unknown number of patients in our study.

Although the fatigue that was measured with the questionnaires resembled one construct, this does not imply that fatigue can only be due to increased transmission failures. Therefore, it would be necessary to study the determinants of fatigue in PPS in general and, for the purpose of our study in particular, in patients with increased neuromuscular transmission defects. This type of preliminary investigation was ignored in our study, but might have resulted in different inclusion criteria that would have ensured the inclusion of only those patients whose overall fatigue was, indeed,

primarily determined by muscle fatigue, and who were therefore more likely to respond to pyridostigmine.

## Benefit of pyridostigmine in sub-groups?

The question that remains is whether there is a sub-group of patients with PPS for whom pyridostigmine would decrease fatigue. The different sub-group analyses described in Chapter 6 did not reveal any evidence for a beneficial effect in patients with large motor units, with reduced quadriceps strength, or with reduced comfortable walking speed. However, in Chapter 7, we found a significant relationship between walking capacity measured in time-scored walking tests and the amount of walking activity in daily life in patients with a limited walking capacity. The highest correlation was found for the test at maximal walking speed: after dichotomizing, the patients with low maximal walking speed walked less in actual daily life, i.e. in their normal environment. In fact, 66% of the variance in their walking activity in daily life was explained by the variance in maximal walking speed ( $P < 0.01$ ). This may imply that the performance of these patients is, to a large extent, determined by their capacity to generate muscle strength, which depends not only on muscle mass, but also on physiological characteristics of the muscle-nerve complex, such as the quality of neuromuscular transmission.

A reduced capacity of muscles to generate strength may have major consequences for daily life activities, especially in patients with severe paresis, because neuromuscular transmission failure may significantly add to their muscle fatigue. In addition, neuromuscular transmission failure in patients with low muscle strength capacity may increase during the execution of a certain task and force the patient to limit certain physical activities (i.e. walking) and, as a result, the amount of walking will decrease.

If the performance of patients with low muscle strength is, indeed, partly due to impaired neuromuscular transmission, then these patients should benefit from pyridostigmine treatment. To test this hypothesis an additional sub-group analysis was performed. A distinction was made between patients with “high” and “low”

walking capacity, based on the group median value of maximal walking speed. Table 1 shows the baseline characteristics of PSS patients with low walking capacity in the walking test at maximal speed. No differences in baseline characteristics were found between the pyridostigmine and placebo-treated patients.

**Table 1** Baseline characteristics, according to treatment group, for PSS patients with low walking capacity in the walking test at maximal speed

| Characteristics / outcome measures  | Pyridostigmine<br>(n=16) | Placebo<br>(n=16)     | <i>P</i> Value |
|---|--------------------------|-----------------------|----------------|
| Age (years)   | 53±9                     | 52±9                  | 0.66           |
| Gender (M/F )   | 5/11                     | 5/11                  | 1.00           |
| Age at polio onset (years)  | 4.5±5.4                  | 2.6±2.8               | 0.23           |
| Duration of PPS symptoms (years)  | 10.1±7.6                 | 10.5±6.6              | 0.86           |
| Severity of paresis of the legs (range 0-32)                                      | 22±5                     | 18±6                  | 0.07           |
| Motor unit size (mV·ms)   | 2.3±1.2 <sup>*</sup>     | 3.5±2.6 <sup>†</sup>  | 0.13           |
| Short Fatigue Questionnaire<br>(range 1-7)  | 5.4±1.1                  | 4.7±1.2               | 0.08           |
| Nottingham Health Profile, energy category<br>(range 0-100)                       | 56±34                    | 46±36                 | 0.41           |
| Fatigue Severity Scale (range 1-7)  | 5.8±0.6                  | 5.7±0.9               | 0.80           |
| Two-minute walking distance, comfortable<br>speed (m)                             | 108±16                   | 98±24                 | 0.20           |
| Maximal walking performance, 75m (s)  | 68±13                    | 77±24                 | 0.20           |
| Walking duration (percentage of total time)                                       | 5.8±3.9 <sup>‡</sup>     | 6.3±2.8 <sup>  </sup> | 0.83           |
| Quadriceps strength (Nm)  | 82±45                    | 77±53                 | 0.76           |
| Maximal voluntary activation (range 0-100)  | 68±18 <sup>¶</sup>       | 69±21 <sup>*</sup>    | 0.82           |
| Muscle fatigability on surface EMG<br>(MF <sub>0-5s</sub> -MF <sub>25-30s</sub> ) | 1.1±2.1 <sup>¶</sup>     | 2.8±3.0 <sup>¶</sup>  | 0.12           |
| Neuromuscular transmission, jitter (μs)   | 40±15                    | 45±16                 | 0.36           |

With the exception of gender, values are presented as mean ± SD. Differences between the two groups were tested with *t* tests ( $\chi^2$  for gender).

<sup>\*</sup>n=13; <sup>†</sup>n=15; <sup>‡</sup>n=5; <sup>||</sup>n=6; <sup>¶</sup>n=14

The results of this sub-group analysis are presented in table 2. They show that when the patients with low maximal walking speed (<50<sup>th</sup> percentile) were treated with pyridostigmine, they improved significantly more in perceived fatigue on the Fatigue Severity Scale (1 scale point,  $P=0.04$ ), in walking capacity (both comfortable [10%,  $P<0.01$ ] and maximal walking speed [5%,  $P=0.03$ ], in maximal quadriceps strength (20%,  $P=0.03$ ), and in maximal voluntary activation (13%,  $P=0.05$ ) than when they were treated with placebo.

The severity of paresis can be used as an indicator of muscle strength, and was calculated as the sum of the strength of 16 lower extremity muscle groups, based on scores from manual muscle testing.<sup>3,11</sup> For the whole study population at baseline, it was found that maximal walking speed was strongly related to this sum score of muscle strength ( $r=0.63$ ;  $P<0.01$ ). Therefore, in the group of patients with low walking capacity, pyridostigmine may have a beneficial effect on fatigue and walking capacity by improving the *limiting factor*, which is muscle strength, as is demonstrated by the significant increase in quadriceps strength and voluntary activation in these patients.

Table 2 also shows that patients with high maximal walking speed (>50<sup>th</sup> percentile) do not benefit from pyridostigmine treatment on any outcome measure. It is unlikely that the significant effects found on five outcome measures (although not on the primary outcome measure), in the sub-group of patients with low walking capacity, while no statistically significant effects were found in the patients with high walking capacity, is merely due to chance resulting from multiple testing or is to be explained by data-fishing.

The percentages of improvements in quadriceps strength and voluntary activation are substantial, but may reflect only small changes in absolute strength.<sup>12</sup> Still, even small changes may have clinical relevance; for some patients it could mean that they regain some of their functional capabilities. Although fatigue measured with the Fatigue Severity Scale improved significantly, fatigue according to the primary outcome measure (Nottingham Health Profile energy category), and muscle fatigability did not improve. This may be due to the methodological limitations of these outcome measures, as described in Chapter 3.

**Table 2** Changes in outcome measures from the second baseline measurements at 14 weeks of treatment, according to treatment group

|   | Sub-group: maximal walking speed at baseline < 4.7 km/h |                          |                      |         | Sub-group: maximal walking speed at baseline > 4.7 km/h |                           |                      |         |
|---|---|--------------------------|----------------------|---------|---|---------------------------|----------------------|---------|
|   | Pyridostigmine  | Placebo                  | $\Delta$ (95% CI)    | P value | Pyridostigmine  | Placebo                   | $\Delta$ (95% CI)    | P value |
|   | (n=16)  | (n=16)                   |                      |         | (n=17)  | (n=15)                    |                      |         |
| Nottingham Health Profile energy cat. (range 0-100)             | -13.3 (37.4)  | -10.4 (31.5)             | -2.9 (-28.3 to 22.4) |         | -22.9 (35.9)  | -23.8 (35.6)              | 0.9 (-25.9 to 27.7)  |         |
| Fatigue Severity Scale (range 1-7)                              | -0.9 (1.0)  | -0.2 (0.8)               | -0.7 (-1.4 to -0.1)  | 0.82    | -0.3 (0.6)  | -0.7 (0.9)                | 0.4 -0.2 to 1.0)     | 0.95    |
| Subjective benefit of treatment                                 | Question 1  | 0.4 (0.8)                | 0.3 (-0.3 to 0.9)    | 0.04    | 0.3 (0.9)   | 0.7 (1.0)                 | -0.5 (-1.2 to 0.2)   | 0.17    |
|   | Question 2  | 0.8 (0.8)                | 0.2 (-0.5 to 0.9)    | 0.34    | 0.2 (0.9)   | 0.5 (0.8)                 | -0.3 (-1.0 to 0.3)   | 0.18    |
| Two-minute walking distance (m)                                 | 13.3 (8.9)  | 3.3 (9.0)                | 10.0 (3.4 to 16.6)   | 0.61    | 7.4 (9.1)   | 3.6 (8.5)                 | 3.8 (-2.9 to 10.4)   | 0.32    |
| Maximal walking performance, 75 m (s)                           | -3.6 (4.1)  | 0.4 (5.2)*               | -4.0 (-7.5 to -0.4)  | 0.004   | 0.3 (3.8)   | -0.1 (2.3)                | 0.4 (-1.9 to 2.8)    | 0.25    |
| Duration of walking (% of total time)                           | 1.5 (1.7) <sup>†</sup>                                  | 1.5 (1.6) <sup>‡</sup>   | 0.0 (-2.3 to 2.2)    | 0.03    | 1.6 (1.0) <sup>‡‡</sup>                                 | -0.1 (1.8) <sup>§§</sup>  | 1.6 (-0.4 to 3.6)    | 0.70    |
| Quadriceps strength (Nm)  | 19.2 (25.2)   | 3.5 (12.2)               | 15.7 (1.4 to 30.1)   | 0.98    | 6.6 (15.7)  | 8.8 (15.1)                | -1.3 (-14.8 to 12.1) | 0.10    |
| Maximal voluntary activation (range 0-100)                      | 11.1 (13.9) <sup>§</sup>                                | -2.0 (14.7) <sup>¶</sup> | 13.1 (0.3 to 26.0)   | 0.03    | 5.1 (14.3) <sup>¶¶</sup>                                | 6.4 (12.3) <sup>‡‡</sup>  | -2.2 (-13.7 to 9.4)  | 0.84    |
| Muscle fatigability (MF <sub>0.5s</sub> -MF <sub>25-30s</sub> ) | 2.1 (3.7) <sup>¶</sup>                                  | 0.4 (3.7) <sup>***</sup> | 1.6 (-1.6 to 4.8)    | 0.05    | -0.1 (2.8) <sup>*</sup>                                 | 0.2 (3.0) <sup>*</sup>    | -0.3 (-2.5 to 2.0)   | 0.70    |
| Neuromuscular transmission, jitter ( $\mu$ s)                   | -9.3 (9.3)  | -1.7 (21.8) <sup>*</sup> | -7.6 (-20.2 to 5.0)  | 0.30    | -2.1 (20.2)   | -4.0 (22.0) <sup>¶¶</sup> | 2.0 (-14.1 to 18.1)  | 0.80    |
|   |   |                          |                      | 0.23    |   |                           |                      | 0.80    |

Results are presented for sub-groups based on the group median value of maximal walking speed. Change is calculated as the scores at intervention minus the scores at baseline and is presented as mean (SD). The difference in change between groups ( $\Delta$ ) is calculated from the change in the pyridostigmine group minus the change in the placebo group and is presented as mean difference (95% confidence interval) and the P value of the t test. \*n=14; <sup>†</sup>n=5; <sup>‡</sup>n=6; <sup>§</sup>n=10; <sup>¶</sup>n=12; <sup>\*\*</sup>n=11; <sup>††</sup>n=9; <sup>‡‡</sup>n=7; <sup>§§</sup>n=3; <sup>¶¶</sup>n=13. CI, confidence interval; MF, median frequency.

However, it could also be due to the fact that, as a result of pyridostigmine treatment, the patients increased their level of daily life activities, i.e. the amount of walking. This would imply that the fatigue itself is not necessarily reduced. However, this remains speculative, due to the lack of sufficient data on daily life activities. In a very small group of only 5 patients with poor maximal walking capacity, no increase was found in walking duration in daily life due to pyridostigmine treatment. It would be interesting to investigate this in a larger group of patients.

The conclusion of this additional sub-group analysis is that patients with low walking capacity, i.e. with more severe paresis resulting in little walking activity in daily life, may benefit from pyridostigmine treatment. Their performance may be strongly determined by their limited capacity to generate muscle strength, which may improve while pyridostigmine improves the neuromuscular transmission.

The walking activity in daily life of patients with greater walking capacity is probably not primarily determined by the capacity to generate muscle strength, but rather by personal and environmental factors. Therefore, an increase in muscle strength, due to improved neuromuscular transmission, will not necessarily change their performance in daily life. Moreover, the transmission disturbances during sustained contractions may not increase during activities for which the demands on the muscle system are relatively low. Thus, transmission defects in these patients may have very little influence on their fatigue and daily behaviour, and these patients are not expected to benefit from pyridostigmine treatment.

Although the above-mentioned sub-group analysis concerning walking capacity was performed after, and in addition to the analyses described in Chapter 6, the results suggest that pyridostigmine can not be ruled out as a treatment option to improve muscle function and performance in some patients with PPS. The clinical relevance of pyridostigmine for PPS patients with poor walking capacity, due to low muscle strength, needs to be confirmed in further studies.

## Encouraging the evaluation of capacities

The severity and the progression of PPS are frequently assessed with measures at the level of muscle function.<sup>13,14</sup> However, Chapters 4 and 6 showed that outcome



measures such as quadriceps strength (measured with a fixed dynamometer), voluntary activation (measured with twitch-interpolation), and neuromuscular transmission defects (measured with S-SFEMG) have a wide variability. They therefore lack the precision to reliably determine the severity of impairments in muscle function, and they lack the sensitivity to identify changes over time, given the usually slow decline in muscle function in patients with PPS.<sup>15,16</sup>

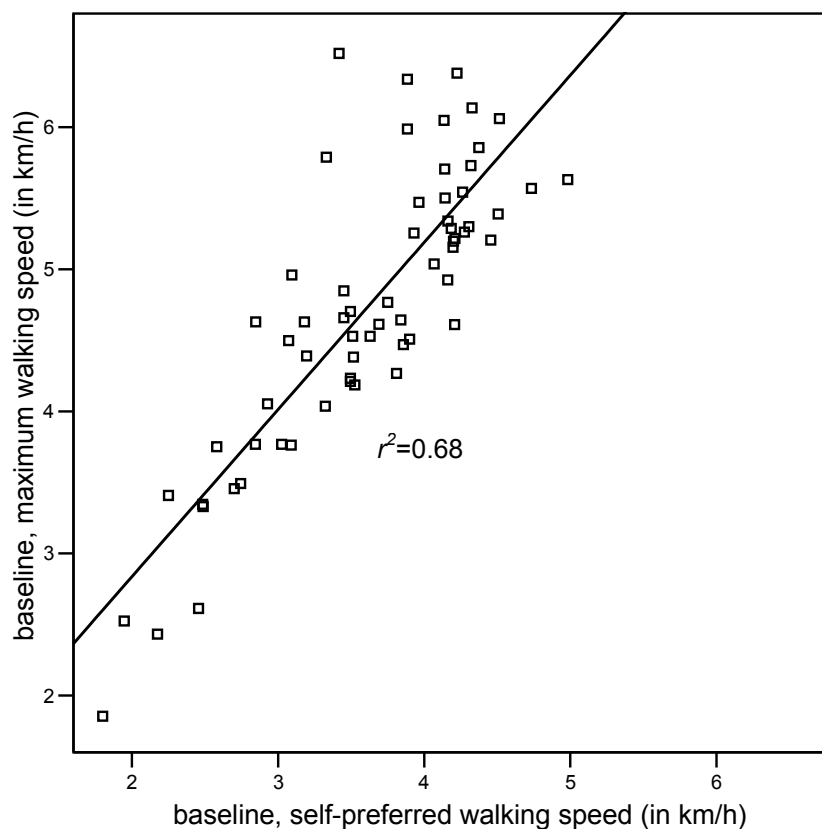
Symptoms and functioning are often assessed with validated questionnaires.<sup>17,18</sup> In our study, questionnaires were used to assess perceived health, fatigue and rating of exertion. Chapters 3 and 5 have shown that the reproducibility of these measures is also poor, and that their ability to detect changes, particularly at individual level, is limited. Apparently, it is difficult to achieve a reliable measurement of function and functioning in patients with PPS. Moreover, there is a wide gap between actual body functions on the one hand, and the perception of functioning of patients on the other hand.

Apart from describing outcome at the level of body functions and structures, outcomes at the level of activity and participation should also be assessed. With regard to the activity and participation level, two important qualifiers are provided in the International Classification of Functioning, Disability and Health (ICF).<sup>19</sup> The *Performance qualifier* describes what an individual does in his or her daily life environment, and the *Capacity qualifier* describes the ability of an individual to carry out activities in a standardized environment, for instance in a test setting.

In our studies, *performance* with regard to walking in daily life was measured with ambulatory accelerometry, and the *capacity* to walk was measured with standardized walking tests. These measurements provided valuable additional information that eventually enabled us to differentiate between patients with PPS who did and who did not respond to pyridostigmine treatment.

In the RCT, walking capacity was measured at self-preferred and at maximal walking speed. Apart from studying the reliability of both walking tests, combining the results from the different studies provided more insight into the validity of these tests, because they supply different information and may therefore serve different purposes. In Chapter 5 it was shown that the two walking tests had good test-retest reproducibility, and that they were sensitive enough to detect relatively small

changes. Since both tests showed equal reproducibility, we concluded that the choice of a test must be based on other arguments. An important argument suggesting that the two tests do provide different information became apparent in the study of the relationships between walking capacity, walking in daily life and perceived mobility problems, as described in Chapter 7. It was found that both walking tests correlated significantly with walking performance in daily life. This was not surprising, since walking at self-preferred speed correlated strongly with walking at maximal speed, explaining 68% of the variance between the results (figure 1).



**Figure 1** Scatter plot of self-preferred versus maximal walking speed at baseline. The squared correlation coefficient ( $r^2$ ) indicates the explained variance in results.

However, it appeared that maximal walking test results in patients with the lowest capacity showed the highest correlation with daily life walking performance ( $r=0.73$ ;  $P<0.01$ ), and an even stronger correlation with walking longer periods ( $>30$  sec) in

daily life ( $r=0.81$ ;  $P<0.01$ )(see Chapter 7). Apparently, the load on the available muscle capacity in walking at self-preferred speed varies between patients, which implies that different patients use different walking strategies. For instance, some patients may walk at a relatively high speed, maybe at the cost of the walking distance, while others walk at a slow speed, using less of the available capacity, and may therefore be capable of walking longer distances. Such inter-individual differences may primarily depend on personal and environmental factors.

An important finding was already addressed earlier in this chapter, namely that maximal walking capacity discriminated between sub-groups with respect to response to pyridostigmine. In view of this trial, which aimed to improve functioning by increasing muscle function, we therefore conclude that maximal walking tests are a better indicator of walking capacity in patients with PPS, and are therefore more preferable than tests at self-preferred speed. However, this does not imply that walking tests at self-preferred speed are of no value; this depends on the purpose of the testing. For example, capacity tests at sub-maximal effort levels could be more appropriate if the aim is to achieve changes at this level, for instance to lower the energy demands of walking at self-preferred speed, to increase self-preferred walking speed, or to increase walking distance.

Our findings emphasize the potential value of capacity outcome measures that evaluate performance in a standardized environment. They may hold an important position between impairments of body functions underlying the disabilities, on the one hand, and daily life functioning on the other hand.<sup>20</sup> First, by relating standardized capacity evaluation to muscle function one can study the impairments in body functions that are responsible for restrictions in functional abilities. This may lead to more specific, and thus more effective intervention strategies. Secondly, by relating standardized capacity evaluation to measurements of performance in daily life and perceived functional problems, one can study the consequences of loss of functional abilities for daily life behaviour and participation.

Therefore, by understanding and developing specific standardized measurements to evaluate capacities, rehabilitation can aim to target interventions at the level of body function and structures or at the level of functional skills, in order to improve the

performance of daily life activities within the environmental and personal context. Measurement of standardized performance should therefore be a key aspect of functional evaluation, and an important outcome in clinical trials.

## Recommendations for future research

The fact that patients with PPS often complain about general fatigue,<sup>9,10</sup> and/or fatigue related to physical activity, such as increased muscle fatigability<sup>21</sup> and delayed recovery,<sup>22</sup> suggests that different forms of fatigue may be present in PPS. To gain more insight into this complex phenomenon of fatigue in PPS, it is therefore necessary to distinguish between the different forms of fatigue. The main question is whether there is one predominant form of fatigue that can be established as the most disabling. Studying the characteristics of different forms of fatigue also provides information about their contribution to the overall fatigue perception, and makes it possible to make comparisons with other illnesses in which fatigue is a major symptom (such as multiple sclerosis) with respect to the relationship between fatigue and the ability to engage in activities, and with respect to strategies to compensate the fatigue.<sup>23</sup>

In addition to distinguishing between the different forms of fatigue in patients with PPS it is also necessary to identify the determinants of (each separate form of) fatigue. It has already been mentioned that there are many possible causes for fatigue in PPS, ranging from global to specific origins.<sup>5-10,24</sup> Knowledge about the determinants of fatigue will not only contribute to our understanding of the origin of fatigue in PPS, but will also give direction to interventions aiming to reduce fatigue in (selected groups of) PPS patients.

Finally, it is also important to study the impact of fatigue on the daily life of patients with PPS. The main objective is to determine the consequences of fatigue on daily life functioning and to investigate whether this impact differs for the various forms of fatigue. Information should be gathered to determine the relationship between fatigue and performance, both in a standardized and in a daily life environment.

To investigate the characteristics, determinants, and impact of different forms of fatigue in patients with PPS a descriptive study in a large unselected population of

patients with PPS is required. Such a study should make a detailed inventory of the characteristics of fatigue and investigate a broad range of potential determinants, including outcomes at the level of muscle function and at the level of performance, both in a standardized and in a daily environment. In particular, attention should be paid to the objective assessment of muscle fatigue. It has already been mentioned that surface and single fibre EMG lack sufficient validity and reliability for this purpose. Efforts should be made to improve such measures. A technique that has recently become available to assess muscle fatigability is <sup>31</sup>P magnetic resonance spectroscopy, which quantifies the chemical status of a muscle by determining concentrations of phosphate metabolites.<sup>5,25</sup> Unfortunately, such measurements are complicated and costly, and are not yet applicable for all muscles.

Earlier in this discussion it was stated that PPS patients with a limited walking capacity improved on pyridostigmine treatment with respect to fatigue, muscle strength and walking capacity. It was suggested that in these patients, in particular, neuromuscular transmission defects might be an important cause of fatigue. A first step in verifying this hypothesis would be to study the change in transmission quality and muscle fatigability during standardized activities, in relation to muscle strength capacity. To study the relationship between fatigue and neuromuscular transmission quality it is necessary to develop a reliable method to measure transmission defects in large lower extremity muscles.

The results of the sub-group analysis encourage further investigation of pyridostigmine treatment in patients with PPS. To determine whether pyridostigmine has a clinically relevant effect on fatigue and functioning in patients with PPS a new trial should be conducted in a larger group of patients with low walking capacity. It could be argued that instead of concentrating on the complex and multi-factor outcome of fatigue, walking capacity should be taken as the primary outcome measure. The advantage of this approach is that walking capacity can be measured with high precision, whereas fatigue may remain unaltered if patients increase their activity levels. Therefore, additional information should be collected on the effect of treatment on activities in the daily life of patients with PPS. To increase the effectiveness of pyridostigmine, the dose should be individually adjusted and

preferably be prescribed in a slow release form to stabilize the plasma concentration throughout the day. Only if such a trial is carried out will we obtain a definite answer to the question of whether or not pyridostigmine is effective in the treatment of selected patients with PPS.

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Summary



In the past it was generally assumed that the residual neurological deficits from polio would remain stable throughout life. However, in the late seventies of the 20<sup>th</sup> century large numbers of polio survivors started to complain about new neuromuscular symptoms. Inventory studies demonstrated that the main symptoms were progressive and persistent (new) muscle weakness, abnormal muscle fatigability, muscle atrophy and muscle and joint pain. These symptoms have been termed the postpoliomyelitis syndrome (PPS). The course of PPS is slowly progressive and negatively affects functioning in daily life. The main problems are fatigue and decreasing physical mobility, which negatively affect the level of independency and decrease life satisfaction.

Poliomyelitis is an infectious viral disease that primarily affects motor neurons and causes an acute, flaccid paresis of a varying number of muscle groups. After the acute polio, motor neurons that have survived the acute stage recover and regain their function. Denervated muscle fibres from permanently lost motor neurons are reinnervated through collateral sprouting from surviving axons, and as a result motor units increase in size. Muscle fibre hypertrophy occurs to compensate for the loss in strength. At the end of recovery, a varying degree of residual paresis remains, providing stable muscle strength and functioning for several decades.

It is supposed that the enlarged motor units following polio do not remain stable throughout life, but degenerate prematurely due to persistent high metabolic stress on the motor neurons. The degeneration of motor units results in a slowly progressive loss of axonal sprouts and consequently, a gradual decline in strength. In addition, it has been suggested that, prior to degeneration of terminal axons, abnormalities in neuromuscular transmission occur, which may cause or increase symptoms such as fatigue and reduced endurance. The presence of transmission defects at the neuromuscular junctions has been confirmed in stimulation single fibre EMG studies.

In 1993 Trojan and Cashman suggested that the transmission defects may partly be due to a defect in the release of the neurotransmitter acetylcholine. To improve the effectiveness of acetylcholine, Trojan and co-workers studied the effect of the anticholinesterase inhibitor pyridostigmine. In a randomised controlled multicenter trial, no effect was found of 180 mg pyridostigmine per day for a period of 6 months

on physical functioning, muscle strength, and fatigue. However, the negative results of this trial may be due to methodological limitations of the study design with respect to patient selection, outcome measures and the dosage of pyridostigmine used.

The letter in **Chapter 2** is a reaction to the results published by Trojan and co-workers and is a critical contemplation of the methodology and design of their trial. The criticism primarily focuses on the lack of responsiveness of the outcome measures and the heterogeneity of the study population. It is concluded that the results of their trial do not exclude pyridostigmine as a possible beneficial treatment for patients with PPS. This conclusion encouraged us to proceed with a randomised trial we had initiated around that time, in which the effect of pyridostigmine on the symptoms of PPS was investigated. In comparison with the trial of Trojan and co-workers, important methodological differences in our study design are that symptom specific outcome measures are applied, a homogeneous patient group is composed, and that the dose of pyridostigmine is raised to 240 mg per day.

**Chapters 3, 4 and 5** report on the validity and reproducibility of the most important outcome measures used in the trial: fatigue questionnaires, maximal muscle strength measurements and walking capacity measurements. In 65 patients with PPS two baseline measurements of fatigue, muscle strength and walking capacity were performed with a 3-week period in between.

Different questionnaires have been used to measure the severity of fatigue in patients with PPS. Comparing results obtained with different questionnaires is problematic, because it is not known whether the differences in scores reflect differences in the severity of fatigue between the study populations or differences in the response characteristics of the questionnaires. In addition, the sensitivity to detect change of questionnaires that measure fatigue in patients with PPS has not yet been described.

In **Chapter 3**, the comparability and reproducibility are investigated of four questionnaires that are frequently used to determine the severity of the fatigue in patients with PPS: The Fatigue Severity Scale (FSS; scale range 1-7), the Nottingham Health Profile (NHP) energy category (scale range 0-100), the Polio

Problem List (PPL) fatigue item (scale range 0-7), and the Dutch Short Fatigue Questionnaire (SFQ; scale range 1-7).

The mean normalised total scores at the second visit were highest (meaning severe fatigue) for the PPL fatigue item ( $81\pm17$ ) and lowest for the NHP energy category ( $47\pm35$ ). The correlations of scores between questionnaires were all significant and ranged from .43 between the NHP energy category and the PPL fatigue item to .68 between the PPL fatigue item and the SFQ. The differences in scores between the questionnaires were significant, except for the difference between the FSS and the PPL fatigue item. Mokken scale analysis to examine construct validity indicated that all questionnaires measured the same unidimensional construct. The reproducibility of the FSS, the PPL fatigue item, and the SFQ was moderate. The smallest detectable change was 1.5 scale points for the FSS, and 2 scale points for the PPL fatigue item and the SFQ.

It is concluded that, for patients with PPS, the questionnaires measure the same fatigue construct, but the score for fatigue, reflecting its severity, may differ considerably as a result of differences in the range for which questionnaires measure fatigue. The moderate reproducibility of the questionnaires indicates a lack of precision, especially when applied at the individual patient level. The choice of the appropriate questionnaire to measure fatigue in PPS may depend on the expected range in the severity of fatigue and the desired responsiveness of the questionnaire.

Long-term studies have estimated the decline in muscle strength in patients with PPS at 1-2% per year. It is questionable whether an individual decline in strength can be identified within several years. There are no data on the ability to detect a change in strength with a fixed dynamometer in individual patients with PPS. In subjects with a history of polio, impaired maximal voluntary muscle activation has been found. Variability in activation will lead to variability in strength, and may therefore contribute to the variability in muscle performance. Therefore, the objectives in **Chapter 4** are to determine what changes in maximal strength can be detected in a symptomatic quadriceps muscle in patients with PPS and to investigate the association between the variability in maximal strength and maximal voluntary activation.

Isometric voluntary peak torque is measured at optimal knee angle, and maximal voluntary activation is determined by twitch interpolation. The difference in strength between the 2 measurements for the whole group was small and not significant. The test-retest reliability was excellent for maximal strength (ICC=.96) and moderate for maximal activation (ICC=.73). The smallest decline in strength that can be detected at group level is 4.5%. However, at the individual level, only a decline in strength larger than 25% can be detected. The mean maximal activation at both visits was 67% of full activation. The variability in maximal activation explained 18% of the variability in maximal strength.

It is concluded that variability in maximal quadriceps strength, measured with a fixed dynamometer, is large and is only partly related to the variability in maximal activation. This implies that even in optimal standardized conditions, it is not possible to detect small changes in the strength of symptomatic quadriceps muscles with a fixed dynamometer in individual patients with PPS. However, the reproducibility is sufficient to evaluate changes in groups of subjects in both follow-up (of more than 4 years) and intervention studies. The limited influence of variability in maximal voluntary activation on the variability in strength may be caused by the curvilinear relationship between voluntary activation and force, and by co-activation of the hamstrings.

Walking capacity is usually measured with timed walking tests. Whether such tests are appropriate to determine a decline in walking capacity depends largely on their reproducibility. Physical effort during walking can be measured objectively by recording the heart rate, but also by rating the perceived exertion. Recently, patients with PPS have been recommended to use a perceived exertion Borg scale in daily life to avoid excessive fatigue. Whether such scale is appropriate for this purpose depends on its stability across measurements and on its relation with the actual effort and performance. **Chapter 5** report on the reproducibility of, and the associations between walking capacity, heart rate, and perceived exertion at self-preferred and maximal walking speed in patients with PPS.

It was found that test-retest reliability of walking capacity was excellent for both tests (ICC range, .94-.97). The smallest detectable change for an individual was 15%

for both tests. Test-retest reliability for heart rate was good (ICC=.86) and moderate for perceived exertion (Spearman  $\rho$  range .67-.70). The smallest detectable change for perceived exertion was between 4 and 6 scale points. The variability in walking capacity was significantly correlated with the variability in heart rate but not with the variability in perceived exertion.

The good reproducibility of both walking tests makes them appropriate to monitor (individual) changes in walking capacity in patients with PPS. Because no difference existed in reproducibility between the tests at different speeds, the choice of test must be based on other criteria. Because of the moderate reproducibility of perceived exertion, it does not seem to be suitable to monitor physical exertion in patients with PPS in order to avoid overloading.

**Chapter 6** describes the results of the randomised, double-blind, placebo-controlled trial on the effect of pyridostigmine on fatigue, physical performance, and muscle function in selected patients with PPS. Sixty-seven ambulatory patients with PPS with increased fatigue and new weakness in one quadriceps muscle showing neuromuscular transmission defects were included. After 2 baseline measurements patients are randomised and treated with pyridostigmine or placebo for 14 weeks. Pyridostigmine is given in a dose of 60 mg four times a day. The primary outcome is fatigue (on the energy category of the Nottingham Health Profile). Secondary outcomes are walking capacity and performance, maximal quadriceps strength and activation, muscle fatigability and neuromuscular transmission defects of the lateral vastus, and the subjective benefit of treatment. The primary data analysis compares the changes from baseline in the outcomes in the 14<sup>th</sup> week of treatment between groups. Motor unit size of the quadriceps is studied as a potential effect modifier.

Thirty-one subjects treated with pyridostigmine and 31 subjects treated with placebo completed the trial. Compliance of medication intake and blinding were sufficient. No significant effect of pyridostigmine was found on fatigue. Walking capacity improved more in the pyridostigmine group than in the placebo group (net improvement of 6.0%;  $P<0.01$ ). Sub-group analysis showed that the significant improvement in walking capacity was only found in patients with normal sized motor units. There was a trend that maximal quadriceps strength improved more in the



pyridostigmine group than in the placebo group (net improvement of 7.2%;  $P=0.15$ ). No effect of pyridostigmine was found on neuromuscular transmission quality, muscle fatigability, and subjective benefit of treatment.

It is concluded that pyridostigmine in the prescribed dose does not reduce fatigue in selected patients with PPS. The significant improvement in walking capacity is less than considered clinically relevant. However, the significant improvement in walking capacity and the trend of improvement in maximal strength suggests that pyridostigmine may have some beneficial effect on physical performance, especially in subjects with neuromuscular transmission defects in normal sized motor units.

The level of effort and the characteristics of walking in tests under standardized conditions may differ from those in daily life when conditions are not standardized. Furthermore, the relationship between walking capacity measured under standardized conditions and actual walking performance in the daily life in patients with PPS has never been investigated. **Chapter 7** compares walking test results with walking in daily life, and investigates the relationships between walking tests, walking activity in daily life, and perceived mobility problems in patients with PPS.

Data are derived from 24 patients with PPS who underwent ambulatory monitoring of their daily life activities (including walking) in the pyridostigmine trial. Walking tests are performed at self-preferred and maximal speed. Heart rate, step cadence and walking speed in the test and in daily life walking are compared. Perceived mobility problems are assessed with the Nottingham Health Profile, category physical mobility.

It was found that heart rate was significantly lower during walking in the test at self-preferred speed than during walking in daily life. No difference in step cadence was found. Self-preferred walking speed in the test correlated significantly with walking speed in daily life. In a sub-group of patients with a walking capacity below the median value, test performance correlated significantly with the duration of walking activity in daily life. No significant correlation was found between perceived mobility problems and walking activity in daily life.

It is concluded that walking in daily life may be more demanding than walking under standardized conditions. Patients do not necessarily adapt their activity pattern

to their perceived mobility problems. Only in patients with low walking capacity, walking capacity influences their daily life walking behaviour.

The discussion in **Chapter 8** critically focuses on the methodology of the randomised clinical trial, discusses the clinical implications of its results, emphasizes the importance of measuring performance in a standardized environment, and gives recommendations for future research. In the trial no relevant beneficial effect of pyridostigmine was found in selected patients with PPS. The negative results can be due to clinimetric limitations of the fatigue questionnaires and the outcome measures of muscle function, as was described in Chapters 3, 4 and 6. However, this is unlikely because no effect was found on any outcome of fatigue, and the mean changes on all outcomes of fatigue and muscle function were small. Another explanation might be that the assumption, on which the trial was based, namely, that the neuromuscular transmission defects are responsible for the increased fatigue, was wrong. There can be several other causes of fatigue, and transmission failures may not have been the primary cause in some patients.

Based on the results presented in Chapter 7, an additional sub-group analysis was performed for walking capacity. It appeared that patients with low walking capacity (<50<sup>th</sup> percentile in the walking test at maximal speed), when treated with pyridostigmine, improved significantly more on fatigue measured with the Fatigue Severity Scale, on both self-preferred and maximal walking speed, and on maximal quadriceps strength and activation, compared to patients who received placebo. No significant effects of pyridostigmine were found in patients with high maximal walking capacity. The walking performance of patients with low walking capacity may be strongly determined by their limited capacity to generate muscle strength, which may improve while pyridostigmine improves the neuromuscular transmission. Therefore, in these patients, pyridostigmine may have a beneficial effect on fatigue and walking capacity by improving the factor that primarily limits physical functioning, i.e. muscle strength. The improvements in strength and voluntary activation are substantial (respectively 20% and 13%) and may have clinical relevance for some patients. The walking performance of patients with greater walking capacity is probably more

determined by personal and environmental factors. These results suggest that pyridostigmine can not be ruled out as a treatment option to improve muscle function and performance in patients with PPS who have little muscle strength (that limits their daily life walking), severe fatigue and demonstrated neuromuscular transmission defects.

Due to the wide measurement variability, at the individual level outcome measures of fatigue and muscle function lack precision to reliably determine the severity of impairments, and lack the sensitivity to identify changes over time. The good test-retest reproducibility of the walking tests, and the significant correlation between walking test results and daily life walking performance (Chapter 7), emphasize the importance of evaluating capacities, i.e. abilities in a standardized environment. Measurements of capacities may hold an important position between impairments of body functions on the one hand, and functioning in daily life on the other hand. Furthermore, in our trial, maximal walking capacity discriminated between sub-groups with respect to response to pyridostigmine. Standardized measurements to evaluate capacities may contribute to a better understanding of the underlying problems, and may provide clues for developing intervention strategies aimed at improving the performance of daily life activities within the environmental and personal context.

Future research should target to gain more insight into the complex phenomenon of fatigue in PPS. Aims should be to investigate whether different forms of fatigue in patients with PPS can be distinguished, to identify the determinants of fatigue (particularly with respect to neuromuscular transmission defects), and to determine the impact of fatigue on daily functioning. To investigate these issues, a descriptive study in a large unselected population of patients with PPS is required. Treatment studies with pyridostigmine should concentrate on patients, whose functional deterioration is primarily caused by transmission defects. The dose of medication should be individually adjusted and outcome measures should focus on the evaluation of performance, both in a standardized and in a daily environment. The clinical relevance of pyridostigmine for PPS patients with poor walking capacity, due to low muscle strength, needs to be confirmed in further studies.

Samenvatting



In het verleden werd aangenomen dat de neurologische restverschijnselen van polio stabiel zouden blijven gedurende het leven. Echter, eind jaren zeventig en begin jaren tachtig van de vorige eeuw uitten grote aantallen voormalige slachtoffers van de polio-epidemieën uit de jaren '40 en '50 klachten over nieuwe neuromusculaire symptomen. Uit inventariserende studies kwam naar voren dat de belangrijkste symptomen waren: nieuwe spierzwakte, abnormale spierversmoegheid, spieratrofie, en spier- en gewrichtspijn. Deze symptomen werden gedefinieerd als het postpoliomyelitis syndroom (PPS). PPS is langzaam progressief en belemmert het dagelijks functioneren. De voornaamste problemen voor patiënten zijn vermoeidheid en afname van fysieke mobiliteit, waardoor de onafhankelijkheid en kwaliteit van leven afnemen.

Poliomyelitis is een infectieziekte die wordt veroorzaakt door het poliovirus dat primair de motorische neuronen in het ruggenmerg aantast. Dit leidt tot een acute, slappe verlamming waarbij een wisselend aantal spiergroepen is aangedaan. Herstel treedt op doordat aangetaste motorische neuronen die de acute fase van polio hebben doorstaan de functie hervatten. Verder treedt reïnnervatie van spiervezels van afgestorven motorische neuronen op door vorming van nieuwe zenuwuitlopers van nog intacte axonen (collaterale sprouting). Dit leidt tot toename van grootte van motor units. Tot slot treedt hypertrofie van spiervezels op waarmee het verlies in spierkracht verder wordt gecompenseerd. Aan het einde van de herstelfase resteert een stabiele parese die gedurende tientallen jaren niet verandert.

Er wordt verondersteld dat de vergrote motor units die zijn ontstaan na de acute polio aanvankelijk stabiel functioneren maar na zo'n 30 tot 40 jaar vroegtijdig degenereren. De hypothese is dat dit het gevolg is van de hoge metabole belasting van de motorische neuronen die immers grote motor units moeten onderhouden. De degeneratie van motor units resulteert in een langzaam progressief verlies van zenuwuiteinden en een geleidelijke afname van spierkracht. Er zijn aanwijzingen dat voorafgaand aan de degeneratie van de zenuwuiteinden neuromusculaire transmissiestoornissen ontstaan, die kunnen leiden tot symptomen zoals toename van vermoeidheid en afname van het uithoudingsvermogen. Studies die gebruik

maakten van stimulatie single-fibre elektromyografie hebben het bestaan van transmissiestoornissen ter hoogte van het motorisch eindplaatje bevestigd.

In 1993 suggereerden Trojan en Cashman dat de transmissiestoornissen het gevolg kunnen zijn van het onvoldoende aanmaken en vrijkomen van de neurotransmitter acetylcholine. Trojan en co-auteurs bestudeerden het effect van de anticholinesteraseremmer pyridostigmine dat de werkzaamheid van acetylcholine verlengt. In de door hen opgezette gerandomiseerde gecontroleerde multicenter studie werd echter geen effect aangetoond van het dagelijks gebruik van 180 mg pyridostigmine gedurende 6 maanden op fysiek functioneren, spierkracht en vermoeidheid. Het negatieve resultaat van deze trial zou echter het gevolg kunnen zijn van methodologische beperkingen met betrekking tot de selectie van patiënten, gekozen uitkomstmaten, en toegepaste dosering van pyridostigmine.

De brief aan de editor van *Neurology* in **hoofdstuk 2** is een reactie op de resultaten gepubliceerd door Trojan en coauteurs en zet kanttekeningen bij de methodologie en het design van hun trial. De kritiek richt zich in het bijzonder op de beperkte responsiviteit van de uitkomstmaten en de heterogeniteit van de patiëntenpopulatie in de studie. In de brief wordt geconcludeerd dat op basis van de resultaten van de trial van Trojan en coauteurs, pyridostigmine niet kan worden uitgesloten als een mogelijk zinvolle behandeling voor patiënten met PPS. Dit was een stimulans om een reeds in voorbereiding zijnde trial naar het effect van pyridostigmine op de symptomen van PPS daadwerkelijk uit te voeren. In vergelijking met de trial van Trojan en coauteurs zijn de belangrijkste methodologische verschillen dat symptoom-specifieke uitkomstmaten zijn toegepast, een homogene patiënten groep is samengesteld en dat de dosering is verhoogd tot 240 mg pyridostigmine per dag.

In de **hoofdstukken 3, 4 en 5** wordt de validiteit en reproduceerbaarheid beschreven van de belangrijkste uitkomstmaten toegepast in de trial: vermoeidheidsvragenlijsten, maximale spierkracht metingen en loopprestatie testen. Bij 65 patiënten met PPS zijn 2 baseline metingen uitgevoerd, met een interval van 3 weken, waarbij vermoeidheid, spierkracht en loopprestatie zijn bepaald.

In het verleden zijn verschillende vragenlijsten gebruikt om vermoeidheid bij patiënten met PPS te meten. Het is een probleem om de resultaten verkregen met verschillende vragenlijsten met elkaar te vergelijken omdat niet duidelijk is of de verschillen in scores daadwerkelijk verschillen in vermoeidheid uitdrukken, of dat ze verschillen in response karakteristieken tussen de vragenlijsten weerspiegelen. Daarnaast is niet bekend wat de gevoeligheid is van vragenlijsten om verandering in vermoeidheid bij patiënten met PPS te detecteren.

In **hoofdstuk 3** is de vergelijkbaarheid en reproduceerbaarheid onderzocht van 4 vragenlijsten die vaak worden gebruikt om de ernst van vermoeidheid bij patiënten met PPS te bepalen: de Fatigue Severity Scale (FSS; schaalbereik 1-7), de Nottingham Health Profile (NHP) categorie energie (schaalbereik 0-100), de Polio Problem List (PPL) item vermoeidheid (schaalbereik 0-7), en de Dutch Short Fatigue Questionnaire (SFQ; schaalbereik 1-7).

De gemiddelde, genormaliseerde totaalscores op de 2<sup>e</sup> baseline meting waren het hoogst (=ernstig vermoeid) voor het PPL item vermoeidheid ( $81 \pm 17\%$  van de schaalrange), en het laagst voor de NHP categorie energie ( $47 \pm 35\%$ ). De correlaties tussen de scores van de vragenlijsten waren allen significant en lagen tussen  $r = .43$  voor de NHP categorie energie en het PPL item vermoeidheid, en  $r = .68$  voor het PPL item vermoeidheid en de SFQ. De vermoeidheidscores verschilden significant tussen de vragenlijsten, behalve tussen de FSS en het PPL item vermoeidheid. Mokken Schaal Analyse ter bepaling van de construct validiteit toonde aan dat alle vragenlijsten hetzelfde unidimensionele construct maten. De reproduceerbaarheid van de FSS, het PPL item vermoeidheid, en de SFQ was matig. De kleinst detecteerbare verandering was 1.5 schaalpunt voor de FSS, en 2 schaalpunten voor het PPL item vermoeidheid en de SFQ.

De conclusie is dat, bij patiënten met PPS, alle vragenlijsten hetzelfde vermoeidheidsconstruct meten, maar dat de score voor vermoeidheid, een maat voor de ernst ervan, aanzienlijk kan verschillen als gevolg van verschillen in bereik waarbinnen de vragenlijsten vermoeidheid meten. De matige reproduceerbaarheid van de vragenlijsten duidt op gebrek aan precisie, vooral wanneer de lijsten worden gebruikt op individueel niveau.



In lange termijn studies is de afname in spierkracht van patiënten met PPS geschat op 1 à 2% per jaar. Het is daarom de vraag of een individuele afname in kracht binnen een periode van slechts enkele jaren kan worden aangetoond. Het is onbekend wat het vermogen van een vaste dynamometer is om een verandering in kracht te detecteren bij (individuen met) PPS. Bij personen die in het verleden polio hebben doorgemaakt is verminderde maximale vrijwillige spier activatie geconstateerd. Variabiliteit in activatie leidt tot variabiliteit in kracht, en kan daardoor bijdragen aan de variabiliteit in spierprestatie. In **hoofdstuk 4** is de kleinst detecteerbare verandering in maximale kracht bepaald in een symptomatische musculus quadriceps van patiënten met PPS, en is de associatie onderzocht tussen variabiliteit in maximale kracht en maximale vrijwillige activatie.

Vrijwillige isometrische piekkracht is gemeten bij een optimale kniehoek, en maximale vrijwillige activatie is bepaald door middel van twitch-interpolatie. Het verschil in kracht tussen de 2 baseline metingen voor de gehele groep was klein en niet significant. De test-hertest betrouwbaarheid was uitstekend voor maximale kracht (ICC=.96) en matig voor maximale vrijwillige activatie (ICC=.73). De kleinste afname in kracht die op groepsniveau (n=65) gedetecteerd kan worden was 4.5%. Op individueel niveau kan een afname van ten minste 25% worden gedetecteerd. De gemiddelde maximale vrijwillige activatie bedroeg 67% van volledige activatie. De variabiliteit in maximale vrijwillige activatie verklaarde 18% van de variabiliteit in kracht.

De conclusie luidt dat de variabiliteit in maximale quadriceps kracht, gemeten met een vaste dynamometer, groot is, en slechts deels gerelateerd is aan de variabiliteit in maximale activatie. Dit impliceert dat, zelfs onder optimale gestandaardiseerde omstandigheden, het met een vaste dynamometer niet mogelijk is om kleine veranderingen in spierkracht in een symptomatische quadriceps van individuele patiënten met PPS te detecteren. De reproduceerbaarheid is wel toereikend om in follow-up studies van ten minste 4 jaar veranderingen in groepen patiënten te kunnen evalueren en om in interventie studies klinisch relevante effecten te kunnen aantonen. De beperkte invloed van variabiliteit in maximale vrijwillige activatie op variabiliteit in kracht kan worden veroorzaakt door de curvilineaire relatie tussen vrijwillige activatie en kracht, of door coactivatie van de hamstrings.

Loopprestatie wordt meestal gemeten met tijdgescoorde looptesten. Of zulke testen geschikt zijn om een afname in loopprestatie te bepalen hangt in grote mate af van hun reproduceerbaarheid. De intensiteit van fysieke inspanning tijdens lopen kan objectief worden gemeten aan de hand van de hartslagfrequentie, maar ook door het scoren van de ervaren belasting. Recentelijk is aanbevolen om patiënten met PPS een Borg schaal te laten gebruiken om ervaren inspanning te scoren met als doel ernstige vermoeidheid te voorkomen. Of een dergelijke schaal geschikt is voor dit doel hangt af van de reproduceerbaarheid en of de scores gerelateerd zijn aan de daadwerkelijke inspanning en prestatie. **Hoofdstuk 5** beschrijft de reproduceerbaarheid van, en de associaties tussen loopvaardigheid, hartslagfrequentie en ervaren inspanning, tijdens looptesten op comfortabele en maximale snelheid in patiënten met PPS.

De test-hertest betrouwbaarheid van loopvaardigheid was uitstekend voor beide testen (ICC range, .94-.97). De kleinst detecteerbare verandering voor een individu bedroeg 15% voor beide testen. De test-hertest betrouwbaarheid was goed voor hartslagfrequentie (ICC=.86) en matig voor ervaren inspanning (Spearman  $\rho$  range .67-.70). De kleinst detecteerbare verandering in ervaren inspanning lag tussen 4 en 6 schaalpunten. De variabiliteit in loopvaardigheid was significant gecorreleerd met de variabiliteit in hartslagfrequentie, maar niet met de variabiliteit in ervaren inspanning.

De goede reproduceerbaarheid van beide looptesten is toereikend om (individuele) veranderingen in loopprestatie van patiënten met PPS aan te kunnen tonen. Omdat de reproduceerbaarheid tussen beide looptesten niet verschilt, kan een eventuele keuze tussen beide testen gebaseerd worden op andere criteria. Vanwege de matige reproduceerbaarheid lijkt een Borg schaal geen geschikt instrument om de mate van fysieke inspanning bij patiënten met PPS te bepalen, en om te gebruiken als methode om overbelasting te voorkomen.

In **Hoofdstuk 6** worden de resultaten gepresenteerd van het gerandomiseerde, dubbelblinde, placebo-gecontroleerde onderzoek naar het effect van pyridostigmine op vermoeidheid, fysieke prestatie en spierfunctie in geselecteerde patiënten met PPS. Zevenenzestig ambulante patiënten met PPS met vermoeidheid en symptomen

van nieuwe spierzwakte in ten minste 1 quadriceps met aangetoonde neuromusculaire transmissiestoornissen, zijn geïnccludeerd. Na 2 baseline metingen worden de patiënten gerandomiseerd en behandeld met pyridostigmine of placebo gedurende 14 weken. Pyridostigmine is gegeven in een dosering van 4 maal daags 60 mg. De primaire uitkomstmaat is vermoeidheid (Nottingham Health Profile, categorie energie). Secundaire uitkomstmaten zijn loopvaardigheid en loopactiviteit, maximale kracht en vrijwillige activatie van de quadriceps, spierversmoegbaarheid en neuromusculaire transmissiestoornissen van de vastus lateralis, en het subjectieve effect van de behandeling. De primaire data-analyse vergelijkt de veranderingen in de uitkomstmaten in de 14<sup>e</sup> week van de behandeling ten opzichte van baseline tussen de groepen. Motor unit grootte van de quadriceps wordt bestudeerd als potentiële effect modifier.

Eenendertig patiënten behandeld met pyridostigmine en 31 patiënten behandeld met placebo voltooiden de trial. De therapietrouw was hoog en de blinding was goed. Er werd geen significant effect van pyridostigmine gevonden op vermoeidheid. De loopvaardigheid verbeterde meer in de pyridostigmine groep dan in de placebo groep (verschil in verbetering: 6%;  $P < 0.01$ ). Subgroepanalyse toonde aan dat alleen patiënten met een normale motor unit grootte significant verbeterden in loopvaardigheid. Er was een trend dat de maximale quadriceps kracht sterker toenam in de pyridostigmine groep dan in de placebo groep (verschil in verbetering: 7.2%;  $P = 0.15$ ). Er werd geen effect van pyridostigmine gevonden op de kwaliteit van de neuromusculaire transmissie, op spierversmoegbaarheid, en op het subjectieve effect van de behandeling.

De conclusie luidt dat pyridostigmine in de voorgeschreven dosering vermoeidheid niet vermindert in geselecteerde patiënten met PPS. De significante verbetering in loopvaardigheid is klein en wordt niet als klinisch relevant beschouwd. Echter, de significante verbetering in loopvaardigheid en de trend van verbetering in maximale kracht suggereren dat pyridostigmine een gering positief effect heeft op fysiek presteren, in het bijzonder in patiënten met neuromusculaire transmissiestoornissen in motor units met een normale grootte.

Het niveau van inspanning en loopkarakteristieken tijdens looptesten onder gestandaardiseerde omstandigheden kunnen afwijken van die in het dagelijks leven waar omstandigheden niet gestandaardiseerd zijn. Daarnaast is de relatie tussen loopvaardigheid, gemeten onder gestandaardiseerde condities, en de daadwerkelijke loopactiviteit in het dagelijks leven niet eerder onderzocht in patiënten met PPS. In **Hoofdstuk 7** worden karakteristieken van lopen in een looptest vergeleken met die tijdens lopen in het dagelijks leven, en wordt de relatie beschreven tussen looptesten, loopactiviteit in het dagelijks leven, en ervaren mobiliteitsproblemen in patiënten met PPS.

Data zijn afkomstig van 24 deelnemers aan de pyridostigmine trial waarbij ambulante metingen zijn verricht van activiteiten in het dagelijks leven (waaronder lopen). Looptesten zijn uitgevoerd op comfortabele en op maximale snelheid. Hartslagfrequentie, stapfrequentie en loopsnelheid in de test en in het dagelijks leven zijn vergeleken. Ervaren mobiliteitsproblemen zijn gemeten met de Nottingham Health Profile, categorie fysieke mobiliteit.

De hartslagfrequentie was tijdens het lopen in de test op comfortabele snelheid significant lager dan tijdens lopen in het dagelijks leven. Er werd geen verschil in stapfrequentie gevonden. De comfortabele loopsnelheid in de test correleerde significant met loopsnelheid in het dagelijks leven. In een subgroep van patiënten met een loopvaardigheid beneden de mediaan correleerde loopprestatie in de tests significant met de duur van loopactiviteit in het dagelijks leven. Er werd geen significante correlatie gevonden tussen ervaren mobiliteitsproblemen en loopactiviteit in het dagelijks leven.

De conclusie is dat lopen in het dagelijks leven mogelijk meer inspanning vergt dan lopen onder gestandaardiseerde omstandigheden. Patiënten passen hun activiteitenpatroon niet onvoorwaardelijk aan aan hun ervaren mobiliteitsproblemen. Loopvaardigheid lijkt alleen invloed te hebben op het dagelijks loopgedrag van patiënten met een verminderde loopvaardigheid.

De discussie in **hoofdstuk 8** evalueert de gebruikte methodologie in de gerandomiseerde klinische trial, bediscussieert de klinische implicaties van de verkregen resultaten, benadrukt het belang van het meten van fysieke prestatie in

een gestandaardiseerde omgeving, en doet aanbevelingen voor toekomstig onderzoek. In de trial is geen klinisch relevant effect van pyridostigmine gevonden in geselecteerde patiënten met PPS. Het negatieve resultaat kan een gevolg zijn van klinimetrische beperkingen van de vermoeidheidsvragenlijsten en de uitkomstmaten voor spierfunctie, zoals is beschreven in de hoofdstukken 3, 4 en 6. Dit is echter onwaarschijnlijk omdat geen enkele uitkomstmaat van vermoeidheid een effect laat zien, en omdat de gemiddelde veranderingen op alle uitkomstmaten van vermoeidheid en spierfunctie gering zijn. Overwogen moet worden of de assumptie waarop de trial was gebaseerd, namelijk, dat neuromusculaire transmissiestoornissen verantwoordelijk zijn voor de ervaren vermoeidheid, juist is. Er zijn meerdere oorzaken voor vermoeidheid beschreven, en transmissiestoornissen hoeven niet de primaire oorzaak te zijn geweest in de PPS patiënten die aan de trial deelnamen.

Gebaseerd op de gevonden samenhang tussen loopvaardigheid en loopactiviteit in het dagelijks leven in hoofdstuk 7, is een aanvullende subgroepanalyse uitgevoerd op basis van loopvaardigheid. Hieruit kwam naar voren dat patiënten met een beperkte loopvaardigheid (<50<sup>ste</sup> percentiel in de looptest op maximale snelheid) behandeld met pyridostigmine, in vergelijking met patiënten behandeld met placebo, significant meer verbeteren in vermoeidheid gemeten met de Fatigue Severity Scale, in zowel comfortabele als maximale loopsnelheid, en in maximale kracht en activatie van de quadriceps. Daarentegen werd geen enkel significant effect van pyridostigmine gevonden bij patiënten met een betere maximale loopvaardigheid (>50<sup>ste</sup> percentiel in de looptest op maximale snelheid). De prestatie van patiënten met een beperkte loopvaardigheid wordt mogelijk sterk bepaald door hun beperkte capaciteit om kracht te leveren. Het is mogelijk dat pyridostigmine door het verbeteren van de neuromusculaire transmissie bij deze patiënten een gunstig effect heeft op vermoeidheid en loopvaardigheid doordat de spierkracht verbetert die in belangrijke mate hun fysiek functioneren bepaalt. De verbetering in kracht en vrijwillige activatie is aanzienlijk (respectievelijk 20% en 13%) en kan als klinisch relevant worden beschouwd. De loopprestatie van patiënten met een betere loopvaardigheid wordt waarschijnlijk meer bepaald door andere factoren dan spierkracht zoals persoonlijke

factoren en omgevingsfactoren. Deze resultaten maken duidelijk dat pyridostigmine niet mag worden uitgesloten als een behandelmogelijkheid om spierfunctie en prestatie te verbeteren bij bepaalde patiënten met PPS. Het betreft die patiënten met dusdanig weinig spierkracht dat het lopen in het dagelijks leven wordt beperkt, en met ernstige vermoeidheid en aantoonbare neuromusculaire transmissiestoornissen.

Als gevolg van de grote variatie in meetresultaten op individueel niveau, missen uitkomstmaten van vermoeidheid en spierfunctie voldoende precisie om de ernst van afwijkingen betrouwbaar te kunnen meten, en zijn ze onvoldoende gevoelig om veranderingen in de tijd te kunnen detecteren. De goede test-hertest betrouwbaarheid van de looptesten, en de gevonden associatie tussen looptestresultaten en loopprestatie in het dagelijks leven (hoofdstuk 7), benadrukken het belang van het evalueren van capaciteiten, ofwel, vaardigheden in een gestandaardiseerde omgeving. Uitkomstmaten op het niveau van capaciteiten kunnen een belangrijke positie innemen tussen stoornissen van lichaamsfuncties aan de ene kant, en het functioneren in het dagelijks leven aan de andere kant. Bovendien blijkt maximale loopcapaciteit in onze trial te discrimineren tussen subgroepen ten aanzien van de effectiviteit van pyridostigmine. Gestandaardiseerde metingen om capaciteiten te evalueren kunnen bijdragen aan een beter begrip van onderliggende problemen, en kunnen handvatten bieden voor het ontwikkelen van interventiestrategieën gericht op het verbeteren van het functioneren in het dagelijks leven, binnen de context van het individu en zijn omgeving.

Toekomstig onderzoek zou als doel moeten hebben meer inzicht te krijgen in het complexe fenomeen van vermoeidheid bij PPS. Doelstellingen daarbij zijn het onderzoeken of verschillende vormen van vermoeidheid bij PPS kunnen worden onderscheiden, het identificeren van de determinanten van vermoeidheid (in het bijzonder met betrekking tot neuromusculaire transmissiestoornissen), en het bepalen van de impact van vermoeidheid op het dagelijks functioneren. Het beantwoorden van deze onderzoeksvragen vereist een beschrijvende studie in een grote niet-geselecteerde populatie van patiënten met PPS. Effectstudies met pyridostigmine zouden zich moeten concentreren op patiënten bij wie de functionele

achteruitgang primair wordt veroorzaakt door transmissiestoornissen. De dosering van de medicatie moet individueel worden afgestemd en uitkomstmaten moeten gericht zijn op het evalueren van fysieke prestaties, zowel in een gestandaardiseerde, als in een dagelijkse omgeving. De klinische relevantie van behandeling met pyridostigmine bij patiënten met PPS met een verminderde loopvaardigheid als gevolg van een lage spierkracht moet worden bevestigd in vervolgstudies.

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About the author



**H**erwin Horemans was born on August 5<sup>th</sup>, 1969 in Etten-Leur, the Netherlands. After attending secondary school in Etten-Leur, he graduated as a physical therapist in 1993 from the Hogeschool West-Brabant in Breda. In 1994, after working as a physical therapist during his military service, he started the study Human Movement Sciences at the Vrije Universiteit in Amsterdam. He did his master's research on hip abductor function in adults treated for Perthes disease at the department of Rehabilitation Medicine of the VU Academic Hospital (currently named as VU University Medical Centre) in Amsterdam. After his graduation in 1998, he started the PhD research project presented in this thesis. Together with dr. Nollet (currently professor and head of the rehabilitation department of the Academic Medical Centre Amsterdam), dr. Beelen (currently senior researcher at the rehabilitation department of the AMC), and prof. Lankhorst, he studied the effect of pyridostigmine on symptoms of the postpoliomyelitis syndrome. In 1999 he obtained a postgraduate degree in epidemiology at the Institute for Research in Extramural Medicine (EMGO-Institute of the Vrije Universiteit). In March 2003 he started working as a research member and manager of the human performance lab at the department of rehabilitation medicine of the Erasmus Medical Centre in Rotterdam. His areas of interest in his present job include gait analysis, physical capacity tests, ambulatory activity monitoring and cerebral palsy. Herwin lives in Leiden, together with his girlfriend Sacha Lamers.



